PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:		(11) International Publication Number: WO 99/0042			
C07K 14/705, C12N 15/12, A61K 38/17, C12Q 1/68	A1	(43) International Publication Date: 7 January 1999 (07.01.99)			
(21) International Application Number: PCT/US (22) International Filing Date: 30 June 1998 (22)	(81) Designated States: CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).				
(30) Priority Data: 60/051,284 30 June 1997 (30.06.97)	τ	Published US With international search report. With amended claims.			
(71) Applicant: PRESIDENT AND FELLOWS OF HACCOLLEGE [US/US]; 124 Mt. Auburn Street, Cambridge MA 02138 (US).					
(72) Inventors: BUCK, Linda; Apartment 2, 27 Dartmou Boston, MA 02116 (US). DULAC, Catherine; 10 Street #48, Cambridge, MA 02138 (US). HE Gilles; 153 Salem Street, Boston, MA 02113 (US SUNAMI, Hiroaki; 15 University Road #31, Brook 02146 (US).	olfe DA, T-				
(74) Agent: PLUMER, Elizabeth, R.; Wolf, Greenfield P.C., 600 Atlantic Avenue, Boston, MA 02210 (U		ks,			
(54) Title: NOVEL FAMILY OF PHEROMONE RECEP	TORS				

(57) Abstract

The invention describes a multigene family encoding a collection of novel mammalian pheromone receptors. Nucleic acids encoding the pheromone receptor polypeptides, including fragments and biologically functional variants thereof are provided. Also included are polypeptides and fragments thereof encoded by such nucleic acids, and antibodies relating thereto. Methods and products for using such nucleic acids and polypeptides also are provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
ΑZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany .	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL FAMILY OF PHEROMONE RECEPTORS

Field of the Invention

5

15

This invention relates to nucleic acids and encoded polypeptides which are part of a multigene family encoding a collection of novel mammalian pheromone receptors. invention further provides representative nucleic acids and encoded polypeptides in this multigene family. The representative polypeptides are expressed in the murine and rat vomeronasal organ (VNO). Agents which bind the nucleic acids or polypeptides also are provided. The invention further relates to methods of using such nucleic acids and polypeptides in the diagnosis and/or treatment of disease, including the use of these molecules in controlling fertility and behavior in vertebrates and invertebrates.

Background of the Invention

Pheromones are intraspecific chemical signals found throughout the animal kingdom. They regulate populations of animals by inducing innate behaviors and stereotyped changes in physiology (Karlson and Luscher, Nature, 1959, 183:55-56; Wilson, Sci. Am., 1963, 208:100-114; Sorensen, Chem. Sens., 1996, 21:245-256). Pheromones can serve as cues for overcrowding, impending danger, reproductive status, gender, or dominance. In rodents, a variety of pheromone effects have been reported. These include effects on estrus and the onset of puberty as well as the induction of mating and aggressive behaviors (Singer, A.G., J. Steroid. Biochem. Molec. Biol., 1991, 39:627-632; Halpern, M., Ann. Rev. Neurosci., 1987 10:325-362; Wysocki, C.J., et al., In the Neurobiology of Taste and Smell, 1987, 125-150; Novotny et al., Chemical signals in Vertebrates, 1990, Vol. 5, eds. D.W. Macdonald et al., Oxford University Press).

The detection of pheromones is mediated by the olfactory system. However, sensory neurons that detect pheromones are typically segregated from those that detect volatile odorants (Keverne, E.B., Trends Neurosci., 1983, 6:381-384; Halpern, M., Ann. Rev. Neurosci., 1987, 10:325-362: Wysocki, C.J., et al., In the Neurobiology of Taste and Smell, 1987, 125-150; Hildebrand, J.G., et al., Brain Res., 1997, 677:157-161). In mammals, sensory neurons in the nasal olfactory epithelium (OE) detect volatile odorants and some pheromones while those in an accessory olfactory organ, called the vomeronasal organ (VNO), are thought to be specialized to detect pheromones. The VNO is a tubular structure, at the base of the nasal septum, which is connected to the nasal cavity by a small duct. Signals from the OE are relayed through the olfactory bulb (OB) to the olfactory cortex, and then to multiple brain regions, including those involved in conscious perception. In contrast, signals from the VNO are conveyed through the

accessory olfactory bulb (AOB) to the amygdala and hypothalamus, areas associated with the

endocrine and behavioral responses induced by pheromones.

20

25

Volatile odorants are detected in the OE by as many as 1000 different types of odorant receptors (ORs), which are differentially expressed by olfactory sensory neurons (Buck and Axel, Cell, 1991, 65:175-187; Levy, N.S., et al., J. Steroid Biochem. Mol. Biol., 1991, 39:633-637, 1991; Nef, P., et al., Proc. Natl. Acad. Sci., 1992, 89:8948-8952; Strotman, J., et al., Neuroreport, 1992, 3:1053-1056; Ngai, J., et al., Cell, 1993, 72:667-680; Ressler, K.J., et al. Cell, 1993, 73:597-609; Vassar, R., et al, Cell, 1993, 74:309-318. The ORs are thought to couple to the G protein a subunit, Gaon thereby initiating a cascade of transduction events which culminate in the generation of action potentials in the sensory axons (reviewed in Firestein, S., Curr. Opin. in Neurobiology, 1992, 2:444-448; Reed, R., Neuron, 1992, 8:205-209; Ronnett, G., et al., Trends Neurosci, 1992, 15:508-513). Current evidence suggests that each OR may recognize a particular molecular feature that can be shared by many odorants (Ressler, K., et al., Cell, 1994, 79:1245-1255; Vassar, R., et al., Cell, 1994, 79:981-991; Axel, R., Sci. Am., 1995, 1273:154-159; Buck, L., Annu. Rev. Neurosci., 1996, 19:517-544). This is consistent with a combinatorial coding model in which the identities of different odorants are encoded by different combinations of receptors, but each receptor serves as one component of the codes for many odorants. By contrast, very little is known about how pheromones are detected or encoded in the VNO. Although VNO neurons (VNs) resemble olfactory sensory neurons in the nose, only a rare VN expresses an OR gene. VNs also lack a number of other olfactory sensory transduction molecules, including the G protein a subunit, Ga_{nt} (Reed, R., Neuron, 1992, 8:205-209), which is highly expressed in olfactory neurons (Dulac and Axel, Cell, 1995, 83:195-206; Berghard, A., et al, Proc. Natl. Acad. Sci. USA, 1996, 93:2365-2369; Wu, Y., et al, Biochem. Biopys. Res. Com., 1996, 220:900-904). Instead, VNs express high levels of two other G protein a subunits, $G\alpha_0$ and $G\alpha i_2$ (Dulac and Axel, Cell, 1995, 83:195-206; Halpern, M., Brain Res., 41995, 677:157-161; Berghard, A., et al, Proc. Natl. Acad. Sci. USA, 1996, 93:2365-2369). G_{**} and $G\alpha i_{*}$ are expressed in spatially-segregated subsets of VNs that form longitudinal zones

15

in the VNO neuroepithelium. Interestingly, Dulac and Axel have identified a family of ~ 100 candidate pheromones receptors ("VNRs") which appear to be expressed exclusively in the $G\alpha i_2$ subset (Dulac and Axel, Cell, 1995, 83:195-206).

This invention differs from the state of the art in providing a novel family of mammalian pheromone receptors. Accordingly, the objects of the invention relate to providing compositions containing these novel receptors and their binding partners and methods for using such compositions to modulate pheromone receptor activity.

Summary of the Invention

The invention involves the discovery of a multigene family of mammalian pheromone receptors. In particular, the invention involves the cDNA cloning of multiple pheromone receptors from a murine VNO cDNA library and from a rat VNO cDNA library. Partial sequences of human homologs of these pheromone receptors also are provided.

In general, the invention provides isolated nucleic acid molecules encoding the novel pheromone receptors, unique fragments of the isolated nucleic acid molecules, expression vectors containing the foregoing, and host cells transfected with the foregoing. The invention also provides isolated pheromone receptor polypeptides and agents which bind such polypeptides, including antibodies. The foregoing can be used in the diagnosis or treatment of conditions, including the control of fertility, that are characterized by the expression of a pheromone receptor polypeptide. Methods for identifying pharmacological agents useful in the diagnosis or treatment of such conditions and methods for identifying additional members of this multigene family also are provided.

Applicants have discovered that the pheromone receptors disclosed herein are expressed in the vomeronasal organ (VNO), particularly in $G\alpha_0$ protein expressing neurons. This is in contrast to the prior art VNO pheromone receptors which are expressed in neurons which express different G-coupled proteins ($G\alpha_1$ -expressing neurons). Thus, the novel pheromone receptors disclosed herein are distinct from, and expressly exclude, the prior art VNO pheromone receptors which differ in primary structure, as well as in cell localization. Although Applicants do not intend the invention to be limited to a particular theory or mechanism, the amino acid sequence homology and structural organization of the pheromone receptor polypeptides to other well-known G-protein coupled receptors suggests that the pheromone receptors disclosed herein also are G-protein coupled. Thus, it is anticipated that the binding to the pheromone receptor of its

15

cognate ligand (pheromone) will be accompanied by G-protein signal transduction, an event which can be measured using conventional screening assays, such as assays that measure changes in the intracellular concentrations of calcium and/or cyclic nucleotides (see, e.g., PCT publication no. WO 94/18959, entitled "Calcium Receptor-Active Molecules", inventors E. Nemeth et al.).

According to one aspect of the invention, a family of pheromone receptor polypeptides is provided. Each polypeptide of the family shares amino acid sequence homology and structural organization with a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. Each polypeptide member of the receptor family contains, from amino terminus to carboxyl terminus, the following domains: (a) an amino-terminal extracellular domain containing from 30 to 600 amino acids; (b) a transmembrane region comprising: (i) seven non-contiguous transmembrane domains designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7, (ii) three noncontiguous extracellular domains designated EC2, EC3 and EC4, and (iii) three non-contiguous intracellular domains designated IC1, IC2, and IC3, wherein the transmembrane domains, the extracellular domains and the intracellular domains are attached to one another from amino terminus to carboxyl terminus in the order TM1-IC1-TM2-EC2-TM3-IC2-TM4-EC3-TM5-IC3-TM6-EC4-TM7, and wherein the transmembrane region has at least about 35% homology and a length approximately equal to a transmembrane region of a polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50; and (c) a carboxyl-terminal intracellular domain containing from 5 to 200 amino acids. Each polypeptide member of the family is expressed in a $G\alpha_0$ protein-expressing vomeronasal organ neuron or are expressed in another olfactory organ neuron in an animal which does not possess a vomeronasal organ. One skilled in the art can readily identify olfactory organs in animals which do not possess a vomeronasal organ.

In general, the amino-terminal extracellular domains (NTDs) of the receptor family members share sequence homology to a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50 to a lesser extent than that observed for the transmembrane region. The length of the extracellular domain can vary among members of the family. Accordingly, certain embodiments of the invention have extracellular domains that contain at least 50, 100, 200, 300, 400 or 500 amino acids. Preferably, the transmembrane region has greater than 40% homology

15

WO 99/00422 PCT/US98/13680

- 5 -

with the corresponding region of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50, and more preferably, have even greater sequence homology (e.g., more than 50%, 60%, 70%, 80% or 90% homology). The length of the carboxyl-terminal intracellular domain can vary among members of the family. Accordingly, certain embodiments of the invention have carboxyl-terminal intracellular domains that contain at least between 5 and 50 amino acids. More preferably, carboxyl-terminal intracellular domains contain between 15 and 25 amino acids.

According to another aspect of the invention, a method for identifying a nucleic acid encoding a pheromone receptor is provided. The method involves contacting a mixture of nucleic acid molecules (genomic library, cDNA library, genomic DNA, RNA, etc.) with at least one nucleic acid probe of a nucleic acid selected from the group consisting of: (a) a nucleic acid molecule selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55 that encodes a pheromone receptor polypeptide; (b) a unique fragment of (a); (c) a human homolog of (a) or (b); and (d) a set of degenerate primers of any of (a), (b) or (c); and identifying the sequences within the mixture that hybridize to the probe. Selected fragments of human homologs of a pheromone receptor are selected from the group consisting of SEQ ID NO. 51, 53, 54 and 55. In certain embodiments, the nucleic acid probe further includes a detectable label to facilitate identification of the sequence in the library which hybridizes to the probe. In certain embodiments, the probe is represented by a pair of degenerate polymerase chain reaction ("PCR") primers that amplify a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55. The meaning of "unique fragment" in reference to a nucleic acid is provided below. By "degenerate PCR primers that amplify a unique fragment" is meant degenerate primers which result in the amplification of a unique fragment following a polymerase chain reaction. According to this embodiment, the method for identifying a nucleic acid encoding a pheromone receptor polypeptide further involves subjecting a mixture of nucleic acids and the degenerate PCR primers to amplification conditions prior to identifying the sequences of the mixture that hybridize to the probe and that form part of the amplification reaction products. In some embodiments the pair of degenerate polymerase chain reaction primers is selected from a conserved sequence motif of a pheromone receptor polypeptide. A "conserved sequence motif" can be determined using the side-by-side comparison of the amino acid sequences of the different

30

pheromone receptor polypeptides of the invention. Exemplary conserved sequence motifs include regions selected from the group consisting of amino acids 191-397, amino acids 565-825, amino acids 637-825, amino acids 637-804, amino acids 619-784, of the polypeptide of, for example, SEQ ID NO. 2 (VR1). In preferred embodiments, the pair of degenerate polymerase chain reaction primers is selected from the group consisting of SEQ ID NOs. 60 and 61, SEQ ID NOs. 62 and 63, SEQ ID NOs. 64 and 63, SEQ ID NOs. 64 and 65, and SEQ ID NOs. 66 and 67.

According to yet another aspect of the invention, an isolated nucleic acid molecule is provided. The isolated nucleic acid molecule hybridizes under high or low stringency conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55. The invention further embraces nucleic acid molecules that differ from the foregoing isolated nucleic acid molecules in codon sequence due to the degeneracy of the genetic code. The invention also embraces complements of the foregoing nucleic acids.

The pheromone receptors of the invention are expressed in the vomeronasal organ or, in an animal which lacks such an organ, are expressed in another olfactory organ. More particularly, the receptors of the invention are expressed in a $G\alpha_0$ protein-expressing vomeronasal organ neuron. Although not intending to be bound to a particular mechanism, it is believed that the receptors of the invention are G-protein coupled receptors. This is supported by Applicants' discovery that the receptors of the invention are expressed in $G\alpha_0$ protein-expressing vomeronasal organ neurons.

The pheromone receptors of the invention bind to ligands (pheromones) which induce certain changes in receptor conformation. Methods for identifying ligands which bind to the pheromone receptors of the invention are provided below, e.g., by forming an affinity matrix containing immobilized receptor and using the matrix to isolate a cognate ligand from a complex mixture. The particular ligand bound by a particular receptor is dictated by the primary and secondary structure of the receptor. In certain embodiments, the immobilized pheromone receptor polypeptide is a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.

According to another aspect of the invention, an isolated nucleic acid molecule that is a unique fragment of any of the foregoing isolated nucleic acid molecules is provided. In general, the isolated nucleic acid molecule consists of a unique fragment between 12 and 4000

25

nucleotides in length, and complements thereof, of any cDNA (SEQ ID NOs. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55) encoding a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. 5 Depending upon its intended use (e.g., probe, primer), the unique fragment can be between 12 and 2000, 1000, 500, 250, 100, 50 or 25 nucleotides in length. Preferably, the isolated nucleic acid molecule consists of between 12 and 35 contiguous nucleotides of the foregoing cDNAs encoding the pheromone receptor polypeptides, or complements of such nucleic acid molecules. More preferably, the unique fragment is at least 14, 15, 16, 17, 18, 20 or 22 contiguous nucleotides of the nucleic acid sequence of the foregoing cDNAs encoding the pheromone receptor polypeptides, or complements thereof. Particularly preferred isolated nucleic acid molecules are isolated fragments of the foregoing cDNAs which encode one or more of the following pheromone receptor polypeptide domains, alone or in combination (e.g., as fusion proteins): an amino-terminal extracellular domain, a transmembrane region, and a carboxyterminal intracellular domain. In certain embodiments, the unique fragments are a pheromone receptor extracellular domain or a pheromone receptor intracellular domain coupled to at least one (e.g., 1, 2, 3, 4, 5, 6, or 7) transmembrane domain.

According to yet another aspect of the invention, an isolated nucleic acid molecule comprising a molecule having a sequence selected from the group consisting of SEQ ID NO. 51, 53, 54, 55, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, and 92, that encodes a pheromone receptor polypeptide are provided. This aspect of the invention further embraces nucleic acid molecules that differ from these nucleic acid molecules in codon sequence due to the degeneracy of the genetic code, and diversity among pheromone receptors and complements of foregoing.

According to still other aspects of the invention, an expression vector comprising any of the foregoing isolated nucleic acid molecules operably linked to a promoter and host cells transformed or transfected with the same also are provided.

According to another aspect of the invention, an isolated polypeptide encoded by any of the above-described isolated nucleic acid molecules is provided. Preferably, the isolated polypeptide is a pheromone receptor polypeptide that has a pheromone receptor activity or an antigenic fragment thereof. As used herein, a pheromone receptor activity refers to the ability of the pheromone receptor to selectively bind to its cognate ligand (pheromone) and, optionally,

10

25

upon binding, to induce signal transduction in a cell that expresses the pheromone receptor. In preferred embodiments, the isolated polypeptide comprises a pheromone receptor polypeptide having a sequence selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.

According to yet other embodiments, the isolated polypeptide comprises a polypeptide encoded by a nucleic acid which hybridizes under high or low stringency conditions to the extracellular domain, transmembrane region and/or intracellular domain of a cDNA sequence selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55 that encodes a pheromone receptor polypeptide or fragment thereof. Thus, the invention embraces portions of a pheromone receptor polypeptide that may include, for example, an amino-terminal extracellular domain or a carboxyterminal intracellular domain coupled to 1, 2, 3, 4, 5, 6, or 7 transmembrane domains. Preferably, such polypeptides or fragments thereof are unique fragments and can function as, for example, antigens for making antibodies specific for pheromone receptor family members. 15 Accordingly, the polypeptides of the invention can be used to isolate additional members of the pheromone receptor family or, alternatively, can be used to induce in vivo an immune response to a pheromone receptor, i.e., can be incorporated into a vaccine preparation. Such vaccine compositions are useful for controlling fertility or behavior in an animal by administering to the animal, an effective amount of the vaccine to elicit an immune response to the pheromone receptor. Thus, the invention embraces fragments or variants of the foregoing pheromone receptors which exhibit certain detectable activities, e.g., a ligand binding activity, an antigenicity activity. In certain embodiments, the isolated polypeptide is encoded by a cDNA selected from the group consisting of SEQ ID NO. 51, 53, 54, 55, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, and 92, that encodes a pheromone receptor polypeptide or one or more of its domains.

According to another aspect of the invention, there are provided isolated binding polypeptides which selectively bind a unique amino acid sequence of a pheromone receptor polypeptide or fragment thereof. The isolated binding polypeptide in certain embodiments binds to a polypeptide comprising the extracellular domain and/or 1, 2, 3, 4, 5, 6, or 7 transmembrane domains of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.

The isolated polypeptide preferably binds to a polypeptide consisting of the aminoterminal extracellular domain and/or one or more portions of the transmembrane region of a pheromone receptor polypeptide sequence selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. In preferred embodiments, isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, $F(ab)_2$, Fd and antibody fragments which include a CDR3 region which binds selectively to the unique sequences of the polypeptides of the invention). In the preferred embodiments, the isolated binding peptides do not bind to pheromone receptors that are expressed in vomeronasal organ neurons other than $G\alpha_0$ -protein-expressing neurons.

10

15

20

25

30

The invention provides in yet other aspects, isolated nucleic acids or polypeptides of the invention that are: (a) immobilized to an insoluble support (an affinity matrix containing immobilized pheromone receptor polypeptide or a unique fragment thereof); (b) associated with, covalently coupled to, or encapsulated a drug delivery device (e.g., a microsphere) to effect controlled release of the isolated nucleic acid or polypeptide in vivo or in vitro; (c) covalently coupled to another isolated nucleic acid or protein to form a chimeric molecule; and/or (d) labeled with a detectable agent (e.g., a radiolabel, a fluorescent label). Thus, the invention provides chimeric molecules containing at least one first structural domain of one pheromone receptor polypeptide (e.g., an extracellular domain) coupled to a second structural domain (e.g., a transmembrane domain, such as TM1, TM2, etc.) of a different pheromone receptor polypeptide. The invention also provides a method for isolating a pheromone receptor by (1) contacting a composition containing a putative pheromone receptor of the above-described family with an affinity matrix containing immobilized binding polypeptide under conditions to permit the pheromone receptor to selectively bind to the immobilized binding polypeptide, and (2) isolating the polypeptides that bind to the affinity matrix.

According to still another aspect of the invention, pharmaceutical compositions containing any of the foregoing compounds of the invention in a pharmaceutically acceptable carrier and methods of producing same by placing the compositions in the carrier also are provided.

According to still another aspect of the invention, methods for modulating a pheromone receptor activity (e.g., a ligand binding activity, a signal transduction activity) in a cell (vertebrate or invertebrate) are provided. The cell can be located in vivo or in vitro and the methods can be used to down regulate (inhibit) or up regulate (stimulate) the pheromone receptor

25

activity. For example, to inhibit a ligand binding activity, the cell is contacted with an inhibitor that can be an isolated binding polypeptide that binds to an extracellular portion of the receptor and, thereby, inhibits receptor binding to its cognate ligand. Such binding also can induce conformational changes in the receptor that alter the signal transduction activity of the receptor. The inhibitor can be an isolated antibody (or function equivalent thereof) which binds to an epitope located on an extracellular portion (such as EC2, EC3, EC4) of the pheromone receptor polypeptide, e.g., an amino-terminal extracellular domain or an "extracellular transmembrane region domain", i.e., an extracellular portion of the transmembrane region located between one or more transmembrane domains. Alternatively, the inhibitor can be an agent (e.g., an isolated competitive binding polypeptide) that inhibits receptor-ligand binding. For example, the inhibitor can be an isolated fragment of a pheromone receptor (preferably, a soluble fragment), which fragment contains a ligand (pheromone) binding site. Other inhibitors can be identified in screening assays which test the ability of a putative inhibitor to inhibit pheromone receptormediated signal transduction or which test the ability of the putative inhibitor to inhibit binding of a pheromone receptor to its known cognate ligand. Similarly, such screening assays can be used to identify molecules which stimulate pheromone receptor-mediated signal transduction. Exemplary molecules which stimulate transduction include the naturally-occurring ligands (e.g., isolated from a biological source (e.g., urine, vaginal fluid), as well as synthetic ligands obtained from a non-biological source (e.g., a combinatorial library).

According to still another aspect of the invention, methods for inhibiting the binding of a pheromone having a binding domain to a pheromone receptor polypeptide having a ligand binding site that selectively binds to the binding domain are provided. The method involves contacting (in vivo or in vitro) the pheromone receptor polypeptide with an agent which binds to the ligand binding site under conditions to permit binding of the agent to the receptor. For example, the agent can be an isolated binding polypeptide that binds to the ligand binding site of the pheromone receptor. Thus, the agent can be an isolated antibody (or functionally equivalent fragment thereof) which selectively binds to the ligand binding site of the receptor. Alternatively, the agent can be a pheromone receptor antagonist, e.g., a molecule that mimics the structure of the naturally-occurring ligand but that does not mimic the function (stimulating the receptor) of the naturally-occurring ligand. Agents which inhibit ligand binding can be identified in screening assays which test the ability of a putative binding inhibitor to inhibit

binding of a pheromone receptor to its cognate ligand (e.g., pheromone). Such molecules can be isolated from a biological source or from a non-biological source.

According to another aspect of the invention, methods for modulating pheromone receptor-mediated signal transduction in a subject are provided. The methods involve administering to a subject in need of such treatment an agent that selectively binds to any of the above-described isolated nucleic acid molecules which encode a pheromone receptor or unique fragment thereof, or an expression product thereof, in an amount effective to modulate (down regulate or up regulate) pheromone receptor-mediated signal transduction in the subject. Exemplary agents include antisense nucleic acid molecules and binding polypeptides.

10

20

Thus, according to yet another aspect of the invention, methods are provided for identifying lead compounds for an pharmacological agent useful in the diagnosis or treatment of a condition associated with pheromone receptor signal transduction activity or otherwise generally associated with binding of the receptor to its cognate ligand. Preferably, cells expressing intact pheromone receptor polypeptides or portions thereof are used in the screening assays for identifying lead compounds which modulate pheromone receptor-mediated ligand binding or signal transduction activity. Cells expressing these polypeptides, isolated pheromone receptor polypeptides and fragments of these polypeptides which contain the ligand binding site can be used in the screening assays for identifying lead compounds which modulate binding of the receptor to a known ligand.

The screening methods involve forming a mixture of a pheromone receptor polypeptide (as noted above) or fragment thereof containing a ligand binding site; a molecule which is known to (1) interact with the foregoing receptor to effect pheromone receptor-mediated signal transduction or (2) bind to the ligand binding site of the receptor; and a candidate pharmacological agent. The mixture is incubated under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of pheromone receptor-ligand binding or receptor-mediated signal transduction by the known ligand. A test amount of the selective binding of the ligand by receptor or of the specific activation of signal transduction is determined. Detection of an increase in the foregoing activities in the presence of the candidate pharmacological agent indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which increases specific activation of pheromone receptor-mediated signal transduction or selective binding of the ligand by the ligand binding site of the receptor. Detection of a decrease in the foregoing activities in the presence of the candidate

15

25

pharmacological agent indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which decreases specific activation of pheromone receptor-mediated signal transduction or selective binding of the ligand by the ligand binding site of the receptor.

Pheromone receptor polypeptides that are useful in the screening assays, preferably, are those selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. Extracellular domains or portions thereof and portions of the transmembrane region, alone or coupled to one another, of these pheromone receptor polypeptides (indicated in the Examples) can be tested for their ability to inhibit receptor-ligand binding.

These and other objects of the invention will be described in further detail in connection with the detailed description of the invention.

All patents, patent publications, references and other information identified in this document are incorporated in their entirety herein by reference.

Brief Description of the Drawings

Figure 1 depicts a comparison of the deduced protein sequences encoded by VR cDNA clones.

Figure 2 is a schematic comparison of ORs, VNRs, and Vrs.

Figure 3 depicts a comparison of the deduced protein sequences encoded by the 20 Go-VN cDNA clones.

Brief Description of the Sequences

SEQ ID NO. 1 is the nucleotide sequence of the mouse pheromone receptor VR1 cDNA (GenBank Accession No. AF011411).

SEQ ID NO. 2 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR1 cDNA (GenBank Accession No. AF011411).

SEQ ID NO. 3 is the nucleotide sequence of the mouse pheromone receptor VR2 cDNA (GenBank Accession No. AF011412).

SEQ ID NO. 4 is the predicted amino acid sequence of the polypeptide encoded by
the mouse pheromone receptor VR2 cDNA (GenBank Accession No. AF011412).

SEQ ID NO. 5 is the nucleotide sequence of the mouse pheromone receptor VR3 cDNA (GenBank Accession No. AF011413).

10

15

20

25

30

SEQ ID NO. 6 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR3 cDNA (GenBank Accession No. AF011413).

SEQ ID NO. 7 is the nucleotide sequence of the mouse pheromone receptor VR4 cDNA (GenBank Accession No. AF011414).

SEQ ID NO. 8 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR4 cDNA (GenBank Accession No. AF011414).

SEQ ID NO. 9 is the nucleotide sequence of the mouse pheromone receptor VR5 cDNA (GenBank Accession No. AF011415).

SEQ ID NO. 10 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR5 cDNA (GenBank Accession No. AF011415).

SEQ ID NO. 11 is the nucleotide sequence of the mouse pheromone receptor VR6 cDNA (GenBank Accession No. AF011416).

SEQ ID NO. 12 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR6 cDNA (GenBank Accession No. AF011416).

SEQ ID NO. 13 is the nucleotide sequence of the mouse pheromone receptor VR7 cDNA (GenBank Accession No. AF011417).

SEQ ID NO. 14 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR7 cDNA (GenBank Accession No. AF011417).

SEQ ID NO. 15 is the nucleotide sequence of the mouse pheromone receptor VR8 cDNA (GenBank Accession No. AF011418).

SEQ ID NO. 16 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR8 cDNA (GenBank Accession No. AF011418).

SEQ ID NO. 17 is the nucleotide sequence of the mouse pheromone receptor VR9 cDNA (GenBank Accession No. AF011419).

SEQ ID NO. 18 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR9 cDNA (GenBank Accession No. AF011419).

SEQ ID NO. 19 is the nucleotide sequence of the mouse pheromone receptor VR10 cDNA (GenBank Accession No. AF011420).

SEQ ID NO. 20 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR10 cDNA (GenBank Accession No. AF011420).

SEQ ID NO. 21 is the nucleotide sequence of the mouse pheromone receptor VR11 cDNA (GenBank Accession No. AF011421).

WO 99/00422 PCT/US98/13680

SEQ ID NO. 22 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR11 cDNA (GenBank Accession No. AF011421).

SEQ ID NO. 23 is the nucleotide sequence of the mouse pheromone receptor VR12 cDNA (GenBank Accession No. AF011422).

SEQ ID NO. 24 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR12 cDNA (GenBank Accession No. AF011422).

5

15

25

SEQ ID NO. 25 is the nucleotide sequence of the mouse pheromone receptor VR13 cDNA (GenBank Accession No. AF011423).

SEQ ID NO. 26 is the predicted amino acid sequence of the polypeptide encoded by
the mouse pheromone receptor VR13 cDNA (GenBank Accession No. AF011423).

SEQ ID NO. 27 is the nucleotide sequence of the mouse pheromone receptor VR14 cDNA (GenBank Accession No. AF011424).

SEQ ID NO. 28 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR14 cDNA (GenBank Accession No. AF011424).

SEQ ID NO. 29 is the nucleotide sequence of the mouse pheromone receptor VR15 cDNA (GenBank Accession No. AF011425).

SEQ ID NO. 30 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR15 cDNA (GenBank Accession No. AF011425).

SEQ ID NO. 31 is the nucleotide sequence of the mouse pheromone receptor VR16 cDNA (GenBank Accession No. AF011426).

SEQ ID NO. 32 is the predicted amino acid sequence of the polypeptide encoded by the mouse pheromone receptor VR16 cDNA (GenBank Accession No. AF011426).

SEQ ID NO. 33 is the nucleotide sequence of the rat pheromone receptor Go-VN1 cDNA (GenBank Accession No. AF016178).

SEQ ID NO. 34 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN1 cDNA (GenBank Accession No. AF016178).

SEQ ID NO. 35 is the nucleotide sequence of the rat pheromone receptor Go-VN2 cDNA (GenBank Accession No. AF016179).

SEQ ID NO. 36 is the predicted amino acid sequence of the polypeptide encoded by
the rat pheromone receptor Go-VN2 cDNA (GenBank Accession No. AF016179).

SEQ ID NO. 37 is the nucleotide sequence of the rat pheromone receptor Go-VN3 cDNA (GenBank Accession No. AF016180).

PCT/US98/13680 WO 99/00422

- 15 -

SEQ ID NO. 38 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN3 cDNA (GenBank Accession No. AF016180).

SEQ ID NO. 39 is the nucleotide sequence of the rat pheromone receptor Go-VN4 cDNA (GenBank Accession No. AF016181).

SEQ ID NO. 40 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN4 cDNA (GenBank Accession No. AF016181).

5

10

15

20

25

SEQ ID NO. 41 is the nucleotide sequence of the rat pheromone receptor Go-VN5 cDNA (GenBank Accession No. AF016182).

SEQ ID NO. 42 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN5 cDNA (GenBank Accession No. AF016182).

SEQ ID NO. 43 is the nucleotide sequence of the rat pheromone receptor Go-VN6 cDNA (GenBank Accession No. AF016183).

SEQ ID NO. 44 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN6 cDNA (GenBank Accession No. AF016183).

SEQ ID NO. 45 is the nucleotide sequence of the rat pheromone receptor Go-VN7 cDNA (GenBank Accession No. AF016184).

SEQ ID NO. 46 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN7 cDNA (GenBank Accession No. AF016184).

SEQ ID NO. 47 is the nucleotide sequence of the rat pheromone receptor Go-VN13C cDNA (GenBank Accession No. AF016185).

SEQ ID NO. 48 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN13C cDNA (GenBank Accession No. AF016185).

SEQ ID NO. 49 is the nucleotide sequence of the rat pheromone receptor Go-VN13B cDNA (GenBank Accession No. AF016186).

SEQ ID NO. 50 is the predicted amino acid sequence of the polypeptide encoded by the rat pheromone receptor Go-VN13B cDNA (GenBank Accession No. AF016186).

SEQ ID NO. 51 is a partial nucleotide sequence of the human pheromone receptor hVR1.

SEQ ID NO. 52 is the predicted amino acid sequence of the polypeptide encoded by the partial sequence of the human pheromone receptor hVR1.

SEQ ID NO. 53 is a partial nucleotide sequence of the human pheromone receptor hVNO1.

PCT/US98/13680 WO 99/00422 - 16 -

SEQ ID NO. 54 is a partial nucleotide sequence of the human pheromone receptor hVNO2.

SEQ ID NO. 55 is a partial nucleotide sequence of the human pheromone receptor hVNO3.

SEQ ID NO. 56 is the nucleotide sequence of primer AL1.

5

15

20

30

SEQ ID NO. 57 is the nucleotide sequence of primer AL3.

SEQ ID NO. 58 is a fifty amino acid sequence of Go-VN13B (SEQ ID NO. 50) that is absent from Go-VN13C (SEQ ID NO. 48).

SEQ ID NO. 59 is the amino acid sequence of a rat kidney extracellular calcium/ polyvalent cation-sensing receptor.

SEQ ID NO. 60 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 61 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 62 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 63 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 64 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 65 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 66 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 67 is a degenerate oligonucleotide primer from a conserved VR domain.

SEQ ID NO. 68 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR1.

SEQ ID NO. 69 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR2.

SEQ ID NO. 70 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR3.

SEQ ID NO. 71 is the nucleotide sequence of the coding region of the mouse 25 pheromone receptor VR4.

SEQ ID NO. 72 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR5.

SEQ ID NO. 73 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR6.

SEQ ID NO. 74 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR7.

WO 99/00422 PCT/US98/13680 - 17 -

SEQ ID NO. 75 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR8.

SEQ ID NO. 76 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR9.

SEQ ID NO. 77 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR10.

5

15

20

25

30

SEQ ID NO. 78 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR11.

SEQ ID NO. 79 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR12. 10

SEQ ID NO. 80 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR13.

SEQ ID NO. 81 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR14.

SEQ ID NO. 82 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR15.

SEQ ID NO. 83 is the nucleotide sequence of the coding region of the mouse pheromone receptor VR16.

SEQ ID NO. 84 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN1.

SEQ ID NO. 85 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN2.

SEQ ID NO. 86 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN3.

SEQ ID NO. 87 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN4.

SEQ ID NO. 88 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN5.

SEQ ID NO. 89 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN6.

SEQ ID NO. 90 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN7.

SEQ ID NO. 91 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN13C.

SEQ ID NO. 92 is the nucleotide sequence of the coding region of the rat pheromone receptor GoVN13B.

5

Detailed Description of the Invention

The present invention in one aspect involves the cloning of cDNAs encoding several members of a multigene family of pheromone receptors. Complete cDNA sequences for selected murine and rat pheromone receptors are provided. Partial sequences of the human gene also are provided. The present invention also relates to the discovery that this family of pheromone receptors is expressed in a $G\alpha_0$ protein-expressing vomeronasal organ neurons (" $G\alpha$ * VNO") or in another olfactory organ neuron in an animal (preferably, a mammal and more preferably, a human) which lacks a vomeronasal organ. Throughout this description, the pheromone receptors of the invention alternatively are referred to as "pheromone receptors", " $G\alpha_0$ * VNO pheromone receptors" or, simply, " $G\alpha_0$ * VNO receptors".

Analysis of the sequence homology between members of the receptor family by comparison to nucleic acid and protein databases established that the pheromone receptor family has several domains. These include, from amino terminus to carboxyl terminus:

(a) an amino-terminal extracellular domain containing from 30 to 600 amino acids; (b) a transmembrane region comprising: (i) seven non-contiguous transmembrane domains designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7, (ii) three non-contiguous extracellular domains designated EC2, EC3 and EC4, and (iii) three non-contiguous intracellular domains designated IC1, IC2, and IC3, wherein the transmembrane domains, the extracellular domains and the intracellular domains are attached to one another from amino terminus to carboxyl terminus in the order TM1-IC1-TM2-EC2-TM3-IC2-TM4-EC3-TM5-IC3-TM6-EC4-TM7, and wherein the transmembrane region has at least about 35% homology and a length approximately equal to a transmembrane region of a polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50; and (c) a carboxyl-terminal intracellular domain containing from 5 to 200 amino acids. Each polypeptide member of the family is expressed in a $G\alpha_0$ protein-expressing vomeronasal organ neuron or are expressed in another olfactory organ neuron in an animal which does not possess a vomeronasal organ. One skilled in the art can readily identify olfactory organs in animals which do not possess a vomeronasal organ. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (ftp://ncbi.nlm.nih.gov/pub/). Exemplary tools include the BLAST system. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVector sequence analysis software (Oxford Molecular Group).

The structure of the $G\alpha_0^+$ VNO pheromone receptors suggests that these receptors are members of the large G protein-coupled receptor superfamily (GPCR). Like other GPCRs, the $G\alpha_0^+$ VNO pheromone receptors exhibit seven hydrophobic stretches ("hydrophobic domains") and are similar in structure to other types of GPCRs, the calcium sensing receptor (CSR Ser. ID No. 59) and the metabotropic glutamate receptors (mGluRs). The CSR and mGluRs are unusual among the GPCRs in that they have extremely long N-terminal extracellular domain (e.g., 557-565 amino acids), a feature that is shared by the pheromone receptors of the invention. Despite this similarity, the receptors of the invention do not share substantial primary structure homology with the CSR and mGluRs. The receptors of the invention also are very different structurally from two other G-protein coupled receptors, the odorant receptors and $G\alpha_{12}^+$ vomeronasal receptors, which share none of the characteristic sequence motifs of the receptors of the invention and, moreover, which have very small (~12-28 amino acids) N-terminal extracellular domains.

The receptors of the invention differ somewhat in amino acid sequence, with regions of relatively high sequence homology. Refer to Examples 1 and 2 for a discussion and illustration of the amino acid sequence homology for the murine and rat $G\alpha_0^+$ VNO receptors, respectively. Other features of these members of the $G\alpha_0^+$ VNO receptor family also are discussed and illustrated in the Examples. For example, signal sequences have been identified for several of the $G\alpha_0^+$ VNO receptors disclosed in the Examples.

Homologs and alleles of the pheromone receptor nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences (SEQ ID NOs. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55) which code for $G\alpha_0^+$ VNO pheromone receptors and which hybridize to a nucleic acid molecule consisting of the coding region of any one $G\alpha_0^+$ VNO pheromone receptor selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52, under high or low stringency conditions. The term "high or low stringency conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found

25

- 20 -

in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, high stringency conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH₂PO₄(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. Low stringency conditions would be the same, but with a lower temperature (e.g., 55°C). After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.2 x SSC/0.5% SDS at temperatures of up to 65°C. Additional conditions of varying stringency are provided in the Examples.

PCT/US98/13680

There are other conditions, reagents, and so forth which can used, which result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the $G\alpha_0^+$ VNO pheromone receptor nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

20

In general homologs and alleles typically will share at least 35% nucleotide identity and/or at least 50% amino acid identity to the cDNAs encoding a $G\alpha_0^+$ VNO pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52, in some instances will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances will share at least 60% nucleotide identity and/or at least 75% amino acid identity. Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention. As discussed above in the Summary of the invention, certain domains within the pheromone receptors may share even greater sequence homology to a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.

10

20

In screening for $G\alpha_0^+$ VNO pheromone receptor polypeptides, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film to detect the radioactive signal.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, in vitro or in vivo, to incorporate a serine residue into an elongating $G\alpha_0^+$ VNO pheromone receptor polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to,: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code. In addition, areas of high similarity among pheromone receptors may differ in amino acid sequences such that they share many, but not all, amino acids. Their nucleotide sequences all differ accordingly.

The invention also provides isolated unique fragments of the cDNAs encoding a $G\alpha_0^+$ VNO polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52, or complements of these sequences. A unique fragment is one that is a 'signature' for the larger nucleic acid. It, for example, is long enough to assure that its precise sequence is not found in molecules outside of the $G\alpha_0^+$ VNO pheromone receptor nucleic acids defined above. Unique fragments can be used as probes in Southern blot assays to identify such nucleic acids, or can be used as primers in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200 nucleotides or more are preferred for certain uses such as Southern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, as demonstrated in the Examples, or for generating immunoassay

components. Likewise, unique fragments can be employed to produce nonfused fragments of the $G\alpha_0^+$ VNO pheromone receptor polypeptides, useful, for example, in the preparation of antibodies, in immunoassays, and as a competitive binding partner of the pheromones and/or other ligands which bind to the $G\alpha_0^+$ VNO pheromone receptor polypeptides, for example, in therapeutic applications. Unique fragments further can be used as antisense molecules to inhibit the expression of $G\alpha_0^+$ VNO pheromone receptor nucleic acids and polypeptides, particularly for the insecticide and other fertility control purposes as described in greater detail below.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of a cDNA selected from the group consisting of SEQ ID NO. 51, 53, 54, 55, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, and 92, that encodes a $G\alpha_0^+$ VNO polypeptide, and its complement will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 bases long). Virtually any segment of the region of the cDNAs encoding the full length $G\alpha_0^+$ VNO polypeptide or their complements, that is 18 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non- $G\alpha_0^+$ VNO pheromone receptor nucleic acids. A comparison of the sequence of the fragment to those on known data bases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

As mentioned above, the invention embraces antisense oligonucleotides that selectively bind to a nucleic acid molecule encoding a $G\alpha_0^+$ VNO pheromone receptor polypeptide, to decrease a pheromone receptor activity (e.g., a ligand binding activity, a signal transduction activity). This is desirable in virtually any condition wherein a reduction in pheromone binding or induction of a behavior that is triggered by pheromone binding is desirable, including to control fertility and behavior in vertebrates and invertebrates. The compositions of the invention are particularly useful in, for example, controlling fertility in livestock and controlling reproduction in rodents or insects by interrupting the normal behaviors of rodents or insects that result in reproduction. As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological

25

30

WO 99/00422 PCT/US98/13680

conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon the cDNA sequences of Examples 1 and 2 (SEQ ID NOs. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55), or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., Nature Biotechnol. 14:840-844, 1996). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to Nterminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In addition, 3'-untranslated regions may be targeted. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., Cell Mol. Neurobiol. 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although, Examples 1 and 2 disclose cDNA sequences (SEQ ID NOs. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55), one of ordinary skill in the art may easily derive the genomic DNA corresponding to the cDNA of these cDNAs. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to a cDNA sequence selected from the group consisting of SEQ ID NOs. 1, 3, 5, 7, 9, 11, 13, 15, 17,

10

19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55. Similarly, antisense to allelic or homologous cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

10

30

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding pheromone receptor polypeptides, together with pharmaceutically acceptable carriers.

Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art.

As used herein, a "vector" may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to, plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g., B-galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein).

15

30

PCT/US98/13680 WO 99/00422 - 26 -

Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably" joined when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

15

20

25

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding pheromone receptor polypeptide or fragment or variant thereof. That heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that

confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1α, which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996).

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

The invention also permits the construction of pheromone receptor gene "knock-outs" in cells and in animals, providing materials for studying certain aspects of pheromone receptor binding, signal transduction activity, or function.

The invention also provides isolated polypeptides, which include a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52 and unique fragments of these pheromone receptor polypeptides. Such polypeptides are useful, for example, alone or as fusion proteins to generate antibodies.

A unique fragment of a pheromone receptor polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52

will require longer segments to be unique while others will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 and 12 amino acids long).

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include interaction with antibodies, interaction with other polypeptides (G-proteins) or molecules (e.g., a ligand) or fragments thereof, selective binding of nucleic acids or proteins, and enzymatic activity. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family members. A comparison of the sequence of the fragment to those on known data bases typically is all that is necessary.

10

15

The invention embraces variants of the pheromone receptor polypeptides described above. As used herein, a "variant" of a pheromone receptor polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a pheromone receptor polypeptide. Modifications which create a pheromone receptor variant can be made to a pheromone receptor polypeptide 1) to reduce or eliminate an activity of a pheromone receptor polypeptide, such as a ligand binding activity or a signal transduction activity; 2) to enhance a property of a pheromone receptor polypeptide, such as protein stability in an expression system or the stability of protein-protein binding; or 3) to provide a novel activity or property to a pheromone receptor polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety. Modifications to a pheromone receptor polypeptide are typically made to the nucleic acid which encodes the pheromone receptor polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and additions of amino acids or non-amino acid moieties. Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the pheromone receptor amino acid sequence.

In general, variants include pheromone receptor polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a pheromone receptor polypeptide by eliminating proteolysis by proteases in an expression system.

Mutations of a nucleic acid which encode a pheromone receptor polypeptide preferably preserve the amino acid reading frame of the coding sequence, and preferably do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such a hairpins or loops, which can be deleterious to expression of the variant polypeptide.

5

10

Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant pheromone receptor polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., E. coli, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a pheromone receptor gene or cDNA clone to enhance expression of the polypeptide. The activity of variants of pheromone receptor polypeptides can be tested by cloning the gene encoding the variant pheromone receptor polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the variant pheromone receptor polypeptide, and testing for a functional capability of the pheromone receptor polypeptides as disclosed herein. For example, the variant pheromone receptor polypeptide can be tested for a ligand binding activity, wherein a ligand to which the receptor binds is contacted with the variant receptor and the amount of ligand binding to the variant receptor is determined using conventional procedures to measure the binding of one molecule to another. Preparation of other variant polypeptides may favor testing of other activities, as will be known to one of ordinary skill in the art.

The skilled artisan will also realize that conservative amino acid substitutions may be made in pheromone receptor polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e, the variants retain the functional capabilities of the pheromone receptor polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring

WO 99/00422 PCT/US98/13680

Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. To a certain extent, the various members of the pheromone receptor family that are illustrated in the Examples represent exemplary functionally equivalent variants of the pheromone receptor polypeptides. Other functionally equivalent variants include conservative amino acid substitutions of the amino acids of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

Conservative amino-acid substitutions in the amino acid sequence of pheromone receptor polypeptides to produce functionally equivalent variants of pheromone receptor polypeptides typically are made by alteration of the nucleic acid encoding pheromone receptor polypeptides. Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method described in Proc. Nat. Acad. Sci. U.S.A. 82: 488-492, 1985, or by chemical synthesis of a gene encoding a pheromone receptor polypeptide. Where amino acid substitutions are made to a small unique fragment of a pheromone receptor polypeptide, such as a ligand binding site peptide, the substitutions can be made by directly synthesizing the peptide. The activity of functionally equivalent fragments of pheromone receptor polypeptides can be tested by cloning the gene encoding the altered pheromone receptor polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered pheromone receptor polypeptide, and testing for a functional capability of the pheromone receptor polypeptides as disclosed herein. Peptides which are chemically synthesized can be tested directly for function, e.g., for binding to a ligand to which the unaltered pheromone receptor is known to bind.

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of the pheromone receptor polypeptides of the Examples. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated pheromone receptor molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise

introduced into cells to cause production of the encoded polypeptide. Translation of mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce polypeptide. Those skilled in the art also can readily follow known methods for isolating pheromone receptor polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The isolation of the pheromone receptor gene also makes it possible for the artisan to diagnose a disorder characterized by expression of pheromone receptor. These methods involve determining expression of the pheromone receptor gene, and/or pheromone receptor polypeptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction as exemplified in the examples below, or assaying with labeled hybridization probes.

The invention also makes it possible to isolate the naturally occurring ligands (pheromones) and other ligands that have a ligand binding domain, namely, by the binding of such molecules to the pheromone receptor polypeptides (or fragments thereof containing a ligand binding site). Binding of the receptors to a ligand can be accomplished by introducing into a biological system in which the proteins bind (e.g., a cell) a molecule that includes a binding domain (putative ligand) in an amount sufficient to detect the binding.

The invention also provides agents such as binding polypeptides which bind to pheromone receptor polypeptides and/or to complexes of pheromone receptor polypeptides and their ligand binding partners. Such binding agents can be used, for example, in screening assays to detect the presence or absence of pheromone receptor polypeptides and complexes of pheromone receptor polypeptides and their ligand binding partners and in purification protocols to isolate pheromone receptor polypeptides and complexes of pheromone receptor polypeptides and their ligand binding partners. Such agents also can be used to inhibit the native activity of the pheromone receptor polypeptides or their ligand binding partners, for example, by binding to such polypeptides, or their binding partners or both.

20

The invention, therefore, embraces peptide binding agents which, for example, can be antibodies or fragments of antibodies having the ability to selectively bind to pheromone receptor polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')₂ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

10

15

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of nonspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

20

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')₂, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric F(ab')₂ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves polypeptides of numerous size and type that bind specifically to pheromone receptor polypeptides, and/or complexes of both pheromone receptor polypeptides and their ligand binding partners. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptoids and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the pheromone receptor polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the pheromone receptor polypeptide. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear portion of the sequence that binds to the pheromone receptor polypeptide can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the pheromone receptor polypeptides. Thus, the pheromone receptor polypeptides of the invention, or a fragment thereof, can be used to screen peptide

libraries, including phage display libraries, to identify and select peptide binding partners of the pheromone receptor polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of pheromone receptor and for other purposes that will be apparent to those of ordinary skill in the art.

A pheromone receptor polypeptide, or a fragment which contains the ligand binding site, also can be used to isolate naturally-occurring ligands and other binding partners of the receptors of the invention. For example, an isolated pheromone receptor can be used to isolate ligands that bind to the receptor binding site by immobilizing a receptor (or fragment containing the ligand binding site) on a chromatographic media, such as polystyrene beads, or a filter, and using the immobilized polypeptide to isolate molecules that bind to this affinity matrix in accordance with standard procedures for affinity chromatography.

It will also be recognized that the invention embraces the use of the pheromone receptor cDNA sequences in expression vectors, as well as to transfect host cells and cell lines, be these prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are oocytes, mammalian cells such as mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. The expression vectors require that the pertinent sequence, i.e., those nucleic acids described *supra*, be operably linked to a promoter.

20

25

5

When administered, the therapeutic compositions of the present invention are administered in pharmaceutically acceptable preparations. Such preparations may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, supplementary immune potentiating agents such as adjuvants and cytokines and optionally other therapeutic agents.

The therapeutics of the invention can be administered by any conventional route, including injection or by gradual infusion over time. The administration may, for example, be oral, intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol. Techniques for preparing aerosol delivery systems containing antibodies are well known to those of skill in the art. Generally, such systems should utilize components which will not significantly impair the biological properties of the antibodies, such as the paratope binding

15

25

capacity (see, for example, Sciarra and Cutie, "Aerosols," in <u>Remington's Pharmaceutical Sciences</u>, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art can readily determine the various parameters and conditions for producing antibody aerosols without resort to undue experimentation. When using antisense preparations of the invention, slow intravenous administration is preferred.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

The preparations of the invention are administered in effective amounts. An effective amount is that amount of a pharmaceutical preparation that alone, or together with further doses, produces the desired response in the condition being treated, e.g., modifying fertility or pheromone-mediated behaviors that are related to reproduction or aggression. For example, this can involve the use of the compounds of the invention as pesticides to slow or halt insect or rodent behaviors that result in reproduction. Alternatively, this can involve the use of the compounds of the invention as agents for controlling fertility in animals (e.g., livestock, domestic animals), by providing compounds which inhibit or stimulate the behaviors in such animals that result in reproduction or agression. This can be monitored by routine methods, e.g., observing the behavior in the animal (vertebrate or invertebrate) recipient.

The invention also contemplates gene therapy, e.g., to prepare an animal model for studying the conditions and behaviors (e.g., fertility, aggression) that are pheromone receptor-mediated. The procedure for performing ex vivo gene therapy is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction in vitro of a functional copy of a gene into a cell(s) of a subject which contains a defective copy of the gene, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered

5

10

cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. In vivo gene therapy using vectors such as adenovirus, retroviruses, herpes virus, and targeted liposomes also is contemplated according to the invention.

The invention further provides efficient methods of identifying pharmacological agents or lead compounds for agents active at the level of a pheromone receptor or pheromone receptor fragment modulatable cellular function. In particular, such functions include ligand binding activity. Generally, the screening methods involve assaying for activation of pheromone receptors or assaying for compounds which interfere with a pheromone receptor activity such as pheromone receptor binding to its cognate ligand. Such methods are adaptable to automated, high throughput screening of compounds. The target therapeutic indications for pharmacological agents detected by the screening methods that block pheromone receptor activity are limited only in that the target cellular function be subject to modulation by alteration of the formation of a complex comprising a pheromone receptor polypeptide or fragment thereof and one or more natural pheromone receptor ligands. Target indications include cellular processes modulated by 15 pheromone receptor signal transduction following receptor-ligand binding.

A wide variety of assays for pharmacological agents are provided, including, labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, cellbased assays such as two- or three-hybrid screens, expression assays, activation of G-proteins, etc. For example, three-hybrid screens are used to rapidly examine the effect of transfected nucleic acids on the intracellular binding of pheromone receptor or pheromone receptor fragments to specific extracellular targets (e.g., ligands in biological samples, such as urine, vaginal fluid, or in combinatorial libraries).

Pheromone receptor fragments used in the methods, when not produced by a transfected nucleic acid are added to an assay mixture as an isolated polypeptide. The assay can be used to screen putative ligands for their ability to bind to the receptor. Pheromone receptor polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts. Recombinantly produced pheromone receptor polypeptides include chimeric proteins comprising a fusion of a pheromone receptor protein with another polypeptide. For example, a polypeptide fused to a pheromone receptor polypeptide or fragment may also provide means of readily detecting the fusion protein, e.g., by immunological recognition or by fluorescent labeling.

In addition to the pheromone receptor, a screening assay mixture includes a binding partner for the receptor, e.g., a naturally occurring ligand that is capable of binding to the pheromone receptor or, alternatively, is comprised of an analog which mimics the pheromone receptor binding properties of the naturally occurring ligand for purposes of the assay. The screening assay mixture also comprises a candidate pharmacological agent (e.g., a putative receptor agonist or antagonist). Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration of agent or at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate pharmacological agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily be modified through conventional chemical, physical, and biochemical means. Further, known pharmacological agents may be subjected to directed or random chemical modifications such as

acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein and/or protein-nucleic acid binding. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate pharmacological agent, the pheromone receptor polypeptide specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other parameters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

10

25

After incubation, the presence or absence of specific binding between the pheromone receptor polypeptide and one or more binding targets is detected by any convenient method available to the user. For cell free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximum signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromatographic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts,

buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of Pheromone receptor polypeptide binding to a target molecule typically encodes a directly or indirectly detectable product, e.g., \(\beta\)-galactosidase activity, luciferase activity, and the like. A wide variety of cell based assays for G-protein coupled receptors could also be employed for detection of molecules that stimulate (agonsists) pheromone receptors or block (agonists) that stimulation by natural ligands or agonists. Pheromone receptor polypeptides or chimeric receptors composed only in-part of a pheromone receptor could be employed in these assays. The chimeric receptors might, for example, contain part of another G-protein coupled receptor such that binding of a ligand to the pheromone receptor binding domain results in coupling to a particular G-protein where activation could be easily assayed. For cell free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc). or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). The label may be bound to a pheromone receptor binding partner (ligand), or incorporated into the structure of the binding partner.

10

20

25

30

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradioactive energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

The invention provides pheromone receptor -specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development, including the development of pesticides and other agents for controlling fertility and reproduction (or related behaviors) in animals. For example, pheromone receptor-specific pharmacological agents are useful in a variety of diagnostic and therapeutic applications, especially where disease or disease prognosis is associated with improper utilization of a pathway involving pheromone receptor. Novel pheromone receptor-specific binding agents include pheromone receptor-specific antibodies and other natural intracellular binding agents

identified with assays such as two hybrid screens, and non-natural intracellular binding agents identified in screens of chemical libraries and the like.

In general, the specificity of pheromone receptor binding to a binding agent is shown by binding equilibrium constants. Targets which are capable of selectively binding a pheromone receptor polypeptide preferably have binding equilibrium constants of at least about 10⁷ M⁻¹, more preferably at least about 10⁸ M⁻¹, and most preferably at least about 10⁹ M⁻¹. The wide variety of cell based and cell free assays may be used to demonstrate pheromone receptor specific binding. Cell based assays include one, two and three hybrid screens, assays in which pheromone receptor -mediated transcription is inhibited or increased activation of G-proteins, etc. Cell free assays include pheromone receptor -protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind pheromone receptor polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced in vitro or in vivo in a host. Such techniques include transfection of nucleic acid-CaPO₄ precipitates, transfection of nucleic acids associated with DEAE, transfection with a retrovirus including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

PCT/US98/13680

Examples

Example 1

20

Experimental Procedures

5 Preparation and analysis of single cell cDNAs

Male mouse (C57BL/6J) VNOs were minced, incubated in Trypsin-EDTA (Gibco-BRL/LTI, Rockville, Maryland), and triturated to obtain dissociated cells. The cells were centrifuged (1000 RPM, 5 min) and resuspended in phosphate buffered saline + 0.1% bovine serum albumin. Individual cells that appeared to be neurons were transferred to separate tubes with a microcapillary pipet.

cDNAs were prepared from each cell and amplified according to Brady and Iscove (*Methods in Enzymology*, 1993, 225:611-621) with minor modifications. Briefly, cDNAs were prepared from the 3' ends of mRNAs by reverse transcription with an oligo (dT) primer, and a poly dA stretch was added to each cDNA with terminal transferase. The cDNAs were then amplified by PCR with one of two primers, AL1 (ATTGGATCCAGGCCGCTCTGGACAA AATATGAA TTC(T) (SEQ. ID. No. 56) (Dulac and Axel, *Cell*, 1995, 83:195-206 or AL3 (GGCACATGG ACGAAATCTTGGTACTCTTCAGAATTC(T), (SEQ. ID. No. 57) and Taq polymerase [Amplitaq LD ("ALD") or Amplitaq Stoffel Fragment ("ASF") (Perkin Elmer, Norwalk, CT)].

Aliquots of each cDNA sample were electrophoresed on agarose gels and blotted onto nylon membranes (Hybond N⁺, Amersham, Piscataway, NJ) (Ausubel, F., et al., *Current Protocols in Molecular Biology*, 1988, John Wiley & Sons NY, NY; Sambrook, J., et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, 1989). The blots were hybridized at 55° or 70°C in Hyb Buffer (0.5M sodium phosphate buffer (pH7.3), 4% SDS, 1% bovine serum albumin (BSA)) with ³²P-labeled probes prepared by random priming (Prime-It II, Stratagene, La Jolla, CA).

Construction and screening of single cell cDNA libraries

An aliquot of cDNA sample VN14 was digested with Eco RI and gel-isolated fragments of 0.1-1.5 kb were cloned into λZapII Ausubel, F., et al., Current Protocols in Molecular Biology, 1988, John Wiley & Sons NY, NY; Sambrook, J., et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989). Two

thousand library clones were plated at low density. Replica filter lifts were hybridized at 75°C (in Hyb Buffer containing 2µg/ml poly (dT)24 and 1µg/ml of random dA-dT 20-mers) to ³²P-labeled probes (~2.5 x 10⁸ CPM/µg; 5 x 10⁶ CPM/ml) prepared by PCR of different single cell cDNA samples. Clones that hybridized to only a VN14 probe were isolated, and a probe prepared from the insert of each was hybridized to blots of selected single cell cDNAs. Clones that hybridized to only VN14 cDNAs were sequenced.

Isolation and analysis of VR cDNA clones

sc153, one VN14*VN2° clone from the VN14 library, was used as probe to screen a mouse VNO cDNA library ('λVNO') (Berghard, A., et al., *J Neurosci*, 1996, 16:909-918) and a mouse genomic DNA library (Stratagene, La Jolla, CA) (70°C, Hyb buffer). Hybridizing clones were found only in the genomic library. A fragment containing 2kb upstream of sc153 was isolated from one genomic clone (153G1) and used to screen lVNO (55°C, Hyb Buffer). The region (D10-TM7) of one clone (D10) that showed homology to TM7 of the CSR (SEQ ID NO. 59) was then used to screen lVNO (55°C, Hyb Buffer), yielding a variety of VR cDNA clones. Additional clones were obtained from lVNO using probes prepared from clones previously isolated, or from PCR products obtained by amplification of mouse genomic DNA or VNO cDNA with degenerate primers (Buck, L., et al., *Cell*, 1991, 65:175-187) matching conserved motifs in the VRs. Some PCR products were also cloned into pCR2.1 (Invitrogen, Carlsbad, CA) and sequenced.

Analysis of VR mRNAs by RT-PCR

20

Random-primed cDNA prepared from male or female C57BL/6J mouse VNO RNAs (or VR cDNA clones) were used in PCR reactions with degenerate primers (Buck and Axel, *Cell* 1991, 65:175-187) matching conserved VR motifs to amplify VR sequences corresponding to amino acids 33-772 in VR1 (SEQ ID NO. 2). Nested PCR was performed with a 1/1000 dilution of the first PCR reaction and primer pairs matching regions of putative exons 1 and 6 in specific VR cDNA clones. Blots prepared from size-fractionated, nested PCR products were hybridized (70°C, Hyb buffer containing 100µg/ml herring sperm DNA (Sigma, St Louis, MO)) to probes prepared from the PCR products of the cDNA clones.

Northern and Southern bl ts and genomic library screens

Northern Blots: One μg of PolyA* RNA prepared from mouse VNO and OE, or purchased from Clontech (other tissue RNAs), was size fractionated on formaldehyde gels, and blotted (see above) (Berghard and Buck, *J. Neurosci*, 1996, 16:909-918). The blot was hybridized (70°C, Hyb Buffer) with a ³²P-labeled probe prepared from the regions of cDNAs VR1, VR2, VR4, and VR15 corresponding to that encoding amino acids 33-772 in VR1 (SEQ ID NO. 1).

Southern Blots: 5 μg of genomic DNA prepared from C57BL6/J mouse liver was digested with Eco RI or Hind III, size fractionated, and blotted (Ressler et al, *Cell*, 1993, 73:597-609). The blots were hybridized (70°C, Hyb buffer containing sperm DNA (see above)) to probes prepared from 3' untranslated segments of different VR cDNA clones [VR2 (nt.2607-2961 of SEQ ID NO. 3), VR3 (nt. 2505-2907 of SEQ ID NO. 5), and VR15 (nt. 3239-3689 of SEQ ID NO. 29)]. A VR4 probe was also used, which gave the same results as highly related VR15 probe.

Genomic library screens to determine VR gene number: A mouse genomic library was screened separately at 70°C or 55°C (see above) with different ³²P-labeled probes. Probe 1: a mix of segments of cDNAs VR1 (SEQ ID NO. 1), VR2 (SEQ ID NO. 3), VR4 (SEQ ID NO. 7), and VR15 (SEQ ID NO. 29) encoding the region corresponding to amino acids 619-772 of VR1 (SEQ ID NO. 2). Probes 2-6: Segments of VR genes obtained from mouse genomic DNA by PCR with degenerate primers matching conserved VR sequence motifs. The PCR segments corresponded to the following amino stretches in VR1 (SEQ ID NO. 2): amino acids 191-397, 565-825, 637-825, 637-804, and 619-784. For example, degenerate oligonucleotide primer pairs used included:

for amino acids 191-397:

5' primer= (GCT)TI(CT)A(CT) CA(AG)(AG)TIGCI(AC)CIAA(AG)GA(CT)AC (SEQ ID NO. 25 60),

3' primer= G(CT)(AG)T(GT)IGCI(AG)(CT)I(AG)C(AG)T(AG)IACI(AG)C(AG)TT (SEQ ID NO. 61);

for amino acids 565-825:

30

5' primer=(AC)(AG)ITG (CT)CCI(GT)AIIA(CT)(AC)A(AG)TA(CT)GCIAA (SEQ ID NO. 62),

3' primer= GIC(GT)IA(CT)IA(AG)IATIA (CT)(AG)TAI(AC)(AT)(CT)TTIGGIAC (SEQ ID NO. 63);

for amino acids 637-825:

5' primer= ATI(AT)(GC)I (CT) TI(AG)TITT(CT)TG(CT)TT(CT)(CT)TITG (SEQ ID NO. 64), 3' primer= GIC(GT)IA(CT)IA(AG)IATIA (CT)(AG)TAI(AC)(AT)(CT)TTIGGIAC (SEQ ID NO. 63);

for amino acids 637-804:

5' primer= ATI(AT)(GC)I(CT)TI(AG)TITT(CT)TG(CT)TT(CT)(CT)TITG (SEQ ID NO. 64), 3' primer=(AG)IATI(GC)(AT)(AG)AAIA(CT)(CT)TCIACI (AG)CIACCAT (SEQ ID NO. 65); and

for amino acids 619-784:

5' primer= GA(CT)ACICCIATIGTIAA(AG)GCIAA(CT)AA (SEQ ID NO. 66), 3' primer= AAIGTIA(CT)CCAIACI(GC)(AT)(AG)CA(AG)AAIAC (SEQ ID NO. 67), wherein all primers are in a 5'→3' direction, I:Inosine.

In situ hybridization

15

20

25

In situ hybridization was performed according to Schaeren-Wiemers and Gerfin-Moser (Histochemistry, 1993, 100:431-440) with sequential 16 micron sections of male or female VNOs. Digoxigenin-labeled cRNA probes were prepared from the same 3' untranslated regions of VR cDNAs as used for the genomic Southern blots. Sections were counter-stained with Hoechst 33258, which labels nuclei. The numbers of G_{so} or G_{si2}-labeled cells (or cells labeled with VR probes) was determined by counting the number of nuclei in labeled regions. The total number of cells was considered to be the sum of G_{so}+ and G_{so}+ cells in adjacent sections.

Chromosome mapping of VR genes

Southern blots of genomic DNA from C57BL/6J and Mus spretus (Jackson Labs) digested with different restriction enzymes were prepared and probed with specific VR cDNA probes as described above. Southern blots of Eco RI, size fractionated genomic DNAs from 94 different backcross mice (M. spretus x (M. spretus x C57BL/6J)), were purchased from Jackson Labs. These blots were hybridized to probes prepared from 3' untranslated segments of the VR2 or VR4 (see above) cDNA at 70°C and washed (see above). Polymorphic bands were typed as 30 either M. spretus or M. spretus/C57BL/6J. The data was sent to the Jackson Laboratory Backcross DNA Mapping Panel Resource for determination of the chromosomal locations of the polymorphic fragments. Additional information was obtained via internet from Jackson Laboratory Mouse Genome Informatics.

Cloning of a gene differentially expressed in G_{so}+ VNs

5

20

25

30

Different members of the OR and VNR families are expressed in different neurons in the OE and G_{si2}+ zone of the VNO, respectively. It therefore appeared likely that the same would be true of sensory receptors expressed by G_{sc}+ VNs. The differential screening of cDNA libraries with cDNA probes prepared from a few neurons can be used to identify genes expressed in one neuron, but not another (Buck, L., et al, *Annu. Rev. Neurosci.*, 1996, 19:517-544). Using PCR, this can be accomplished with single cells (Brady, G., et al., *Methods in Enzymology*, 1993, 225:611-621; Dulac, C., et al., *Cell*, 1995, 83:195-206).

To search for genes encoding receptors expressed by G_{ao} + VNs, we looked for genes expressed in one G_{ao} + VN, but not another, using the PCR-based differential screening approach. In initial experiments, we isolated a series of mouse VNs, prepared cDNAs from the 3' ends of mRNAs present in each, and amplified the single-cell cDNA fragments by PCR. Many of the amplified, single-cell cDNA samples hybridized to an OMP probe, confirming their derivation from VNs (Berghard et al, *Proc. Natl. Acad. Sci. USA*, 1996, 93:2365-2369). With one exception, G_{ao} and G_{ai2} probes hybridized to different OMP+ samples, allowing us to identify samples that were derived from G_{ao} + VNs.

We next prepared a library from one of the $G_{\infty}+$ single-cell cDNA samples (VN14), and isolated clones that hybridized to a probe prepared from VN14, but not to a probe prepared from another $G_{\infty}+$ sample (VN2). We identified 3 VN14+VN2- clones, which differed in size, but were otherwise identical in sequence. None contained an open reading frame, which was not surprising since, in the method used, the amplified cDNAs are only ~400-800 bp long, and are derived from the 3' ends of mRNAs (Brady and Iscove, *Methods in Enzymology*, 1993, 225:611-621).

We next hybridized one of the VN14+VN2- clones (sc153) to the original panel of single-cell cDNAs. sc153 hybridized to VN14, but not to any of the other cDNA samples. Consistent with this result, sc153 hybridized to only a small percentage (~0.3%) of VNs in VNO tissue sections.

Using sc153 as probe, we were able to isolate a sc153+ clone from a mouse genomic library which contained ~2 kb of DNA 5' to the sc153 sequence. Using this 2kb fragment as

5

15

20

probe, we isolated a matching clone (D10) from the VNO cDNA library. Sequence analysis showed that sc153 and D10 were derived from the same gene, but that the D10 cDNA was truncated at the 3' end and did not contain the final 685 bp of sequence present in sc153. Like sc153, D10 hybridized to only a small percentage of VNs in VNO tissue sections.

The 5' end of the D10 cDNA contained a short open reading frame, which encoded a protein fragment with homology to transmembrane domain 7 (TM7) of the calcium sensing receptor (CSR), a G protein-coupled receptor (GPCR) (Brown et al, *Nature*, 1993, 366:575-580). When the TM7-related region of D10 (D10-TM7) was hybridized at reduced stringency (55°C) to the original panel of single-cell cDNAs, it labeled many of the G_{10} + samples, but none of G_{10} + ones (except the one that was also G_{10} +, and was probably derived from two cells). Since D10 labeled only a small percentage of VNs in tissue sections under high stringency conditions, this suggested that many G_{10} + neurons express a gene related to D10, but not identical to it.

A novel multigene family encoding VNO receptors

Hybridization of D10-TM7 to the VNO cDNA library at reduced stringency yielded a number of related cDNA clones (e.g. VR1-VR3, SEQ ID NOs. 1-6). Additional related cDNAs were obtained by RT-PCR with degenerate primers (e.g. VR6-VR7, SEQ ID NOs. 11-14), or by screening the VNO cDNA library with a PCR product obtained from genomic DNA (e.g., VR4, VR5, SEQ ID NOs. 7-10).

These cDNAs encode a novel family of proteins, which are members of the G protein-coupled receptor (GPCR) superfamily (Figure 1). Like other GPCRs, these VNO receptors (VRs) have 7 hydrophobic stretches that may serve as membrane spanning domains. Only 287 of 850 residues are identical in all of the molecules shown in Figure 1, indicating that the family is diverse. The VRs are related to two other types of GPCR, the calcium sensing receptor (CSR) and the metabotropic glutamate receptors (mGluRs) (Tanabe, Y., et al., *Neuron*, 1992, 8:169-179; Brown, E., et al., *Nature*, 1993, 366:575-580). The most highly related molecule is the CSR; for example, VR1 is 31% identical to rat CSR (Riccardi et al., *Proc. Natl. Acad. Sci. USA*, 1995, 92:131-135), with the highest homology residing in the TM1-TM7 region (44%) (Figure 1). However, the VRs comprise a distinct family of receptors, which share novel sequence motifs, and are more related to one another than they are to other receptors. For example, two divergent VRs, VR1 (SEQ ID NO. 1, 2) and VR4 (SEQ ID NO. 7, 8), are 70% identical in TM1-TM7, and 48% identical overall.

The VRs are unusual among GPCRs in having an extremely long N-terminal extracellular domain (Figures 1 and 2). This feature is shared by the CSR and mGluRs, and by an unrelated class of GPCRs that includes several receptors for glycoprotein hormones (Segaloff, D., et al., Oxf. Rev. Reprod. Biol., 1992, 14:141-168). Importantly, the VRs are very different from both ORs and VNRs, which are also GPCRs (Buck. L., et al., Cell, 1991 51:127-133; Dulac, C., et al., Cell, 1995, 83:195-206). VRs share none of the characteristic sequence motifs of ORs or VNRs. In addition, the size of the N-terminal extracellular domain of VRs (557-565 amino acids) far exceeds that of ORs and VNRs (~12-28 amino acids) (Figure 2). The VRs are most variable in the N-terminal domain (25% identical residues compared to 57% in TM1-TM7). In the structurally-related mGluRs, the ligand binding site is thought to reside in the large N-terminal domain (O'Hara et al., Neuron, 1993, 11:41-52; Takahashi et al, J. Biol. Chem., 1993, 268:19341-19345). If this is also true of VRs, the accentuated diversity of the N-terminal domain may reflect an ability to recognize diverse pheromonal ligands.

Most of the VR cDNAs that we analyzed appeared to belong to one of three subfamilies of highly related molecules. For example, VR1 (SEQ ID NOs. 1, 2), VR2 (SEQ ID NOs. 3, 4), and VR3 (SEQ ID NOs. 5, 6) are very similar as are VR4 (SEQ ID NOs. 7, 8) and VR5 (SEQ ID NOs. 9, 10), and VR6 (SEQ ID NOs. 11, 12) and VR7 (SEQ ID NOs. 13, 14) (Figure 1). Nonetheless, our results indicate that all of these cDNAs were derived from different genes. First, all cDNAs were sequenced on both strands to rule out sequencing errors. Second, the RNA used for library construction and PCR came from an inbred mouse strain (C57BL/6J), so they cannot be allelic variants. Third, the error rates of reverse transcriptase (or Taq polymerase) cannot account for the extent to which the cDNAs differ. For example, VR4 (SEQ ID NOs. 7, 8) and VR5 (SEQ ID NOs. 9, 10) cDNAs are 99% identical in nucleotide sequence, but the reverse transcriptase used to prepare them has an error rate of only 3.6 x 10-5/bp (Ji, J., et al., Biochemistry, 1992, 31:954-958).

Variant forms of VR mRNA

25

Many of the VRs we characterized lacked a segment of the N-terminal domain present in other VRs. Invariably, the missing segment corresponded to a region of the human CSR encoded by a single exon, or pair of exons (Pollak, M., et al., Cell, 1993, 73:1297-1303). We also found several different VR cDNAs that contained a stretch of noncoding sequence at a site corresponding to a CSR exon-intron boundary (e.g. VR15). This suggested that the exon-intron

WO 99/00422

structure of VR genes resembles that of the CSR gene, and that variant forms of VR mRNAs might be generated by differential RNA splicing.

Variant VR mRNAs could derive either from different genes, or from the same gene by alternative RNA splicing. Consistent with the latter possibility, two pairs of cDNAs that we sequenced VR8 (SEQ ID NOs. 15, 16) and VR9 (SEQ ID NOs. 17, 18), and VR10 (SEQ ID NOs. 19, 20) and VR11 (SEQ ID NOs. 21, 22) were identical in nucleotide sequence, but were missing different segments. However, when we used RT-PCR to amplify VNO mRNA sequences encoding 5 different VRs, we obtained one major PCR product in each case, regardless of whether the RNA used was from male or female mice. In 4 cases, the size of the major product corresponded to a complete VR, even though one of the cDNAs (but not the PCR product) contained an intron (#5). In one case, in which the cDNA lacked one exon (#2), the major PCR product was even smaller, and was found to lack two exons. Although PCR products of a smaller size were also seen in these experiments, they were much less abundant.

These results suggest that different VR forms derive from different genes. Thus many VR genes may be expressed pseudogenes, which either lack one or more exons, or have mutations that prevent proper RNA splicing. We cannot exclude the possibility that some variant VRs are functional, however. For example, some truncated VRs that lack transmembrane domains could conceivably be secreted pheromone-binding proteins.

20 Differential expression of VR genes in VNO neurons

To investigate the tissue distribution of VR gene expression, we conducted Northern blot analyses in which size fractionated polyA⁺ RNAs from different mouse tissues were hybridized to a mix of radiolabeled VR cDNAs. The mixed probe hybridized to VNO RNAs of ~1.9-3.7 kb, with intense hybridization to RNAs of 2.8-3.5 kb. It did not hybridize to RNAs from a variety of other tissues, including olfactory epithelium and brain. This suggested that VR genes may be expressed exclusively in the VNO.

We found two partial cDNAs that were highly related to VR cDNAs in the NCBI dbEST database, one from spleen and the other from 2-cell stage mouse embryos. However, when we hybridized the most highly related VR cDNAs (VR6 and VR7) to spleen sections, only one questionably-labeled cell was seen out of ~1.4 x 10° cells with one VR probe, and none was seen with the other. The EST clones might be DNA contaminants, or be due to the widespread, but low level, misexpression of tissue specific genes (Sarkar, G., et al., *Science*, 1989, 244:331-334);

- 49 -

nonetheless, we cannot exclude the possibility that VR genes are expressed at a low frequency in some other tissues.

To examine the patterns of expression of different VR genes in the VNO, we conducted in situ hybridization experiments. Labeled segments of the 3' untranslated regions of three VR cDNAs were hybridized separately, or in combination, to sequential sections through the VNO. Probes prepared from G_{ω} and G_{ω} cDNAs were hybridized to adjacent sections to delineate the G_{ω} + and G_{ω} + zones of the VNO neuroepithelium.

The G_{so} and G_{si2} probes gave patterns of hybridization similar to those we had previously seen (Berghard, A., et al, *J. Neurosci.*, 1996, 16:909-918). The G_{so} probe hybridized to a wavy stripe of VNO neurons in the basal (lower) region of the VNO neuroepithleium, whereas the G_{si2} probe hybridized to an adjacent stripe of neurons in the apical (upper) part of the neuroepithelium. The waviness of the two zones appears to be caused by the periodic presence of blood vessels near the base of the epithelium (Berghard, A., et al, *J. Neurosci.*, 1996, 16:909-918). Approximately 57% of VNs were labeled by the G_{si2} probe and 43% were labeled by the G_{si2} probe. The single layer of supporting cells located just beneath the epithelial surface was not labeled by either probe.

Each of the VR probes hybridized to a small percentage (2.4-5.7%) of VNs that appeared to be restricted to the basal, G_{ω} + zone of the VNO neuroepithelium. Labeled neurons were scattered throughout the anterior-posterior and dorsal-ventral extent of the G_{ω} + zone. Small clusters of labeled cells were somtimes seen, particularly with the VR2 probe The mixed probe labeled a larger percentage of VNs (10.6%) that was almost equal to the sum of the percentages labeled by its individual components (10.8%). Thus different G_{ω} + neurons must express different VRs.

No differences were seen in the patterns of hybridization obtained using VNOs from male and female mice, and no hybridization was observed in the nasal olfactory epithelium using either the mix of VR probes or a full-length VR cDNA probe (not shown). Subsequent analyses of the size of the VR gene family, and the number of VR genes recognized by the VR in situ hybridization probes, allowed us to estimate the number of VR genes expressed by individual neurons (see below).

10

To investigate the size of the VR gene family, we hybridized several different mixed VR gene probes to a mouse genomic library, using high (70°C) or low (55°C) stringency conditions. A probe prepared from the membrane spanning regions (putative exon 6) of several different cDNA clones hybridized to 59 and 98 clones per haploid genome equivalent, at high and low stringency, respectively. To obtain probes that were potentially more diverse, we amplified internal segments of putative exon3 or 6 from genomic DNA by PCR with degenerate primers. At high stringency, these probes hybridized to 60-140 clones per haploid equivalent. These results indicate that there are as many as 140 VR genes in the mouse genome.

The VR probes that we used for in situ hybridization each labeled a small percentage of neurons. To determine how many VR genes each probe recognized, we hybridized probes prepared from the same VR cDNA segments to Southern blots of C57BL/6J mouse genomic DNA which had been digested with Eco RI or Hind III. Each probe hybridized to a small number of restriction fragments. Given the small size of the probes (~350-450 bp), most of these fragments should represent at least one gene, provided that there are no introns in the region probed. Consistent with this assumption, the VR2 (SEQ ID NO. 3) probe hybridized to 7 different restriction fragments, as many as five of which could be accounted for by characterized VR cDNAs that were 91-98% identical to VR2 (SEQ ID NO. 3) in the region probed.

Given the number of genes recognized by each VR probe and the percentage G_{∞} + neurons that hybridized to each, we estimate that each VR gene may be expressed in only ~1.1-1.9% of G_{∞} + VNs. Since there appear to be 60-140 VR genes in the mouse genome, this suggests that each G_{∞} + VNO neuron may express only one, or at most a few, VR genes.

Linkage of chromosomal clusters of VR and OR genes

30

We previously found that there are clusters of OR genes at multiple chromosomal sites in the mouse genome (Sullivan, S., et al., *Proc. Natl. Acad. Sci.*, 1996, 93:884-888). To investigate the chromosomal locations of VR genes, we used the Jackson Laboratory Backcross DNA Mapping Panel, which allows the mapping of mouse genes using interspecies mouse crosses.

Probes prepared from the 3' untranslated regions of VR2 (SEQ ID NO. 3) or VR4 cDNAs were first hybridized to Southern blots of genomic DNAs from two mouse species, C57BL/6J and Mus spretus, which had been digested with different restriction enzymes. Eco RI digests showed a number of restriction length polymorphisms with both VR probes. The VR probes

- 51 -

were then hybridized to Eco RI-digested DNAs from a large panel of different backcross mice ((C57BL/6J x M. spretus) x M. spretus).

PCT/US98/13680

The patterns of inheritance of the polymorphic fragments recognized by the two VR probes allowed us to assign chromosomal locations to approximately 9 VR genes. Using the VR4 (SEQ ID NO. 7) probe, we could follow the inheritance of 4 polymorphic restriction fragments. All of these cosegregated in the backcrosses, and mapped to the proximal end of chromosome 7 (near *D7Bir5*). Five restriction fragments were followed for the VR2 (SEQ ID NO. 3) probe. Again, all of the restriction fragments cosegregated, allowing us to map the VR2 (SEQ ID NO. 3) fragments to the distal end of chromosome 4 (near *D4Bir1*). Given the resolution of the genetic mapping, the cosegregating fragments can be no more than 3.8 cM from one another. These results indicate that VR genes are located near the ends of at least two different mouse chromosomes. They also indicate that highly related VR genes are clustered at the same chromosomal locus, as previously seen in our studies and others (Ben-Arie et al, *Human Molecular Genetics*, 1994, 3:229-235.).

The VR4 gene subfamily appears to be closely linked to one OR gene locus, (olfR5) (Sullivan, S., et al., Proc. Natl. Acad. Sci., 1996, 93:884-888). Although the VRs and ORs were mapped in different mouse crosses, the synaptotagmin-3 gene (Syt3) was mapped in both crosses, allowing an estimate of their relative positions. The OR locus mapped 15.05 cM proximal to Syt3 while the VR4 gene cluster mapped 14.89 cM proximal to Syt3. (Jackson Laboratory Mouse Genome Informatics), suggesting a close linkage between VR and OR genes at the proximal end of chromosome 7. Our previous studies indicate that multiple OR gene loci arose via a series of duplications of very large chromosomal domains that maintained linkages between OR genes and members of other gene families. These results therefore suggest that VR genes and OR genes might have been linked in a primitive ancestor. They also suggest the possibility that additional clusters of VR genes might be linked to other OR gene loci.

Example 2

15

25

30

Experimental procedures

Preparation of cDNA Libraries from Isolated VNO Neurons

VNOs were dissected from adult (7- to 8-week-old) male Lewis rats (Sprague-Dawley). Single-cell cDNA synthesis and amplification were performed and checked according to Dulac and Axel (Cell, 1995, 83:195-206). Southern blot analysis of single-cell cDNA was used to

- 52 -

PCT/US98/13680

detect expression of tubulin, OMP, Go, and $Gi_{2\alpha}$ (Dulac and Axel, *Cell*, 1995, 83:195-206). Eighteen cDNAs showed strong hybridization with tubulin and OMP probes, indicating that they originated from mature neurons, and were selected for further study. Cells VN3 and VN13 exhibited high levels of Go expression, whereas VN10 showed presence of $Gi_{2\alpha}$, indicating the origin of these cells from two distinct regions of the VNO neuroepithelium. VN13 single-cell cDNA library was prepared according to Dulac and Axel (*Cell*, 1995, 83:195-206).

Differential Screening of Single-Cell Library

10

30

Plaque-forming units (12 x 10³) from the VN13 library were plated at low density, and duplicate filters (Hybond N⁺, Amersham) were hybridized with probes generated from VN10 and VN13 single-cell cDNAs, following the procedure described in Dulac and Axel, *Cell*, 1995, 83:195-206. Ten phage plaques were detected that showed a positive signal unique to the VN13 probe. These plaques were purified, and the corresponding phage inserts were amplified by PCR, run on 1.5% agarose gel, blotted onto nylon filter, and hybridized with the VN10, VN3, and VN13 single-cell cDNA probes.

Isolation and Analysis of Full-Length cDNA Clones

A 425 bp clone, Go-VN13A, present at the frequency of 0.1% in the VN13 single-cell cDNA library, was selected and in vivo excised to generate the pBlueScriptSK(-) phagemid. High stringency (65°C) screening of a cDNA library prepared from female rat VNO (Dulac and Axel, Cell, 1995, 83:195-206) with the Go-VN13A cDNA probe led to the isolation of Go-VN13B (SEQ ID NO. 49), presenting 90% sequence homology with Go-VN13A. Phages (7.2 x 10⁵) of the female rat VNO library were further screened with the Go-VN13B (SEQ ID NO. 49) cDNA probe under low stringency conditions: hybridization was carried out at 55°C for 24 hr, and the filters were washed three times at 55°C for 30 min in 0.5x SSC and 0.5% SDS. A total of 75 positive phages were identified and the corresponding inserts were amplified by PCR and analyzed by Southern blot using the Go-VN13B (SEQ ID NO. 49) probe at both high (65°C) and low (55°C) stringency. This led to the identification of 22 cDNA clones with insert sizes longer than 3 kb. Among those, six distinct subfamilies were defined by absence of cross-hybridization under stringent conditions of hybridization and washing. Full-length clones (Go-VN1 to Go-VN6, SEQ ID NOs. 33, 35, 37, 39, 41, 43), each representative of a subfamily, were selected for *in vivo* excision and sequenced. Go-VN13C (SEO ID NO. 47) and Go-VN13B

(SEQ ID NO. 49) are identical sequences differing by a 150 bp deletion in Go-VN13C (SEQ ID NO. 47). This sequence encodes for NMDQCANCPEYQYANTEKNKCIQKGVIVLSYEDPLGMALALIAFCFSAFTV (SEQ ID NO. 58) in Go-VN13B (SEQ ID NO. 49) and is replaced by an M at position 552 in Go-VN13C (SEQ ID NO. 48).

DNA Sequencing and Sequence Analysis

DNA sequencing was performed using ABI Prism dye terminator cycle ready reaction (Perkin Elmer, Norwalk, CT) according to manufacturer's protocol. Samples were run on an ABI Prism 310 Genetic Analyzer (Perkin Elmer, Norwalk, CT). Sequence homologies were determined using the BLAST system (NIH network service). Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis were obtained with the MacVector sequence analysis software (Oxford Molecular Group).

15 In Situ Hybridization Analysis

25

In situ hybridization was performed as described elsewhere (Schaeren-Wiemers, N., et al., *Histochemistry*, 1993, 100:431-440). VNOs were dissected from adult male (8- to 9-week-old), adult female (9- to 11-week-old), and young (1-week-old) rats. Tissues were embedded in Tissue-Tek OCT. Antisense and sense digoxigenin-labeled probes were generated from the full-length cDNAs encoding for Go, Gi_{2x}, Go-VN13B (SEQ ID NO. 49), and Go-VN1 to Go-VN6 (SEQ ID NOs. 33, 35, 37, 39, 41, 43), as well as from the 3' untranslated regions of the Go-VN1 to Go-VN6 clones.

Imaging Processing and Statistical Analysis

Digital photographs were captured with a Leitz DMRB microscope (Leica) coupled to a ProgRes3012 digital camera (Kontron Electronic) and further processed with the Photoshop (Adobe System) and Canvas (Deneba) software for Macintosh. The relative positions of cells exhibiting a positive signal by in situ hybridization were measured along the basal-apical axis using the NIH Image analysis software. The number of cells in hemiconcentric sections of 10% along this axis from the basal (value = 0) to the apical (value = 100) boundaries was determined. Average data for Go-VN1 and Go-VN3 to Go-VN6 were obtained from six to eight VNO sections, corresponding to four individuals analyzed in two independent experiments. For

Go-VN2, 14 VNO sections, corresponding to ten individuals and four independent experiments, were analyzed for each sex.

- 54 -

Southern Blot Analysis of Rat Genomic DNA and Screening of Rat and Human Genomic Libraries

Genomic DNA, prepared from Lewis rat (Sprague-Dawley) liver, was digested with the restriction enzymes EcoRI and BamHI, size fractionated on 0.8% agarose gels, and blotted onto nylon membrane (Sambrook, J., et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, 1989). Membranes were cross-linked under UV light, hybridized overnight at both high (68°C) and low (55°C) stringency in hybridization buffer, and washed as described above. ³²P-labeled probes were generated by random priming, using the following DNA templates: EcoRI-EcoRV, NotI-NsiI, EcoRI-SalI, PstI-NdeI, XbaI-HincII, and EcoRI-NsiI fragments of Go-VN1 to Go-VN6 (SEQ ID NOs. 33, 35, 37, 39, 41, 43), respectively; a full-length (425 bp) insert of Go-VN13A; and a cDNA fragment including the seven transmembrane domains of Go-VN13B (SEQ ID NO. 49). Plaque-forming units (3 x 10⁵) from rat and human genomic libraries (Stratagene, La Jolla, CA) were screened at low stringency (55°C) using a mix of ³²P-labeled probes prepared from fragments of Go-VN1 to Go-VN6 (SEQ ID NOs. 33, 35, 37, 39, 41, 43) encompassing the transmembrane domains 2 to 7.

20

5

Results

The VNO Neuroepithelium Expresses Two Independent Families of Pheromone Receptors

We hypothesized the existence of two distinct families of genes encoding pheromone receptor genes that are selectively colocalized with either the Go protein in the basal half of the vomeronasal neuroepithelium or with the $Gi_{2\alpha}$ protein in the apical region. For simplicity of nomenclature, and with the understanding that the cosegregation of distinct G-protein subunits with independent families of pheromone receptors is consistent but does not demonstrate a functional link, the family of genes encoding putative pheromone receptors that we have previously identified and that colocalize with $Gi_{2\alpha}$ will be named $Gi_{2\alpha}$ -VN, whereas the novel family of receptors coexpressed with Go and described in this study will be named Go-VN. In the absence of information concerning the nature of the Go-VN receptor molecules, we reiterated the cloning strategy that allowed us to identify a family of putative pheromone receptor genes

- 55 -

expressed by Gi_{2a}+ neurons (Dulac and Axel, Cell, 1995, 83:195-206). This strategy was based on the assumption that individual neurons within the VNO are likely to express only one pheromone receptor gene and that transcripts encoding a given receptor represent between 1% and 0.1% of a single-cell mRNA. Differential screening of cDNA libraries constructed from single-VNO neurons takes advantage of the fact that different cells express different receptors and thus provides an experimental solution to the problem of detecting a specific transcript in a heterogeneous population of neurons. In this attempt, we expected that differential screening of a cDNA library prepared from an isolated Go+, Gi_{2a}- VNO neuron would permit the isolation of a class of pheromone receptor genes distinct from the Gi_{2a}-VN family of receptor genes.

A cDNA library prepared from a Go+ neuron (VN13) was differentially hybridized with ³²P-labeled probes prepared from VN13 and from a second VNO neuron cDNA (VN10). A 425 bp cDNA (Go-VN13A) present at a frequency of 0.1% in the VN13-cDNA library showed selective hybridization with VN13 cell probe. Two cDNAs of longer size, Go-VN13B (SEQ ID NO. 49) and Go-VN13C (SEQ ID NO. 47), were subsequently isolated from a cDNA library prepared from dissected adult VNOs and showed 90% sequence similarity with Go-VN13A. Hybridization to VNO cross-sections with digoxigenin-labeled antisense RNA probe showed that expression of these transcripts is restricted to a small subpopulation of VNO neurons in a location consistent with the region of Go expression of the neuroepithelium. The sequence of Go-VN13B (SEQ ID NO. 49) reveals a partial open reading frame that includes seven hydrophobic stretches of 20 amino acids in length. Go-VN13B (SEQ ID NO. 49) sequence does not share any resemblance with the odorant receptor genes nor with the family of putative pheromone receptor genes previously identified (see below). In addition, hybridization of Go-VN13B DNA probe to genomic DNA identified two discrete bands at high stringency and 13 or more at lower stringency, revealing the existence of a family of closely related genes in the rat genome.

Taken together, these data indicate that we have isolated a novel multigene family encoding seven transmembrane domain receptors and expressed by subsets of VNO neurons from the basal half of the neuroepithelium.

30 Sequences of a New Family of VNO Receptors

10

25

Recombinant phages from a VNO cDNA library were screened at low stringency with the Go-VN13B (SEQ ID NO. 49) DNA probe. Six distinct gene subfamilies were isolated that

showed no cross-hybridization under stringent conditions of hybridization and washing. cDNAs Go-VN1 to Go-VN6, each representative of a subfamily, were fully sequenced (SEQ ID Nos 33, 35, 37, 39, 41 and 43).

In Go-VN1 to Go-VN5 cDNAs (SEQ ID Nos 33, 35, 37, 39 and 41), the first methionine of the open reading frame was tentatively chosen as a start for protein translation, revealing large open reading frames ranging from 548 to 866 amino acids. A frame shift in the Go-VN6 (SEQ ID NO. 44) sequence (amino acid 532; indicated by slash bar in Fig. 3) indicated that this transcript is unable to generate a functional protein.

Deduced Amino Acid Sequences of cDNAs from the Go-VN Family of Pheromone Receptors

The deduced amino acid sequences of eight cDNAs belonging to the Go-VN family of putative pheromone receptors is shown in Figure 3. Predicted position of seven transmembrane domains is also indicated (I-VII). Amino acids common to at least five cDNAs are shaded. Amino acids common to the rat mGluR1 and Ca2+-sensing receptors are indicated by a star.

Hydropathy analysis of the predicted Go-VN proteins with the Kyte-Doolittle algorithm identified a large hydrophilic N-terminal domain that ranges in size from 274 amino acids in Go-VN1 (SEQ ID NO. 34) to 595 in Go-VN4 (SEQ ID NO. 40). This is preceded in cDNAs Go-VN4 (SEQ ID NO. 40), Go-VN7 (SEQ ID NO. 46), and Go-VN13C (SEQ ID NO. 50) by an initial hydrophobic 21 amino acid segment characteristic of eukaryotic signal sequences. A cluster of seven hydrophobic regions representing potential membrane-spanning helices and typical of the G protein-coupled receptor superfamily is followed by a short hydrophilic sequence that indicates a potential intracytoplasmic C-terminal domain. A database search indicated the presence of sequence motifs common to Ca2+-sensing and metabotropic glutamate (mGluR) receptors (Houamed, K., et al., Science, 1991, 252:1318-1321; Masu, M., et al., Nature, 1991, 349:760-765; Brown, E., et al., Nature, 1993, 366:575-580; Pollak, M., et al., Cell, 1993 75:1297-1303). Pairwise sequence alignments reveal 18% to 23% sequence identity between the rat Ca2+-sensing receptor and the most distant (Go-VN3, SEQ ID Nos.37, 38) and the closest (Go-VN1, SEQ ID NOs. 33, 34) Go-VN sequences, respectively. Sequences of rat mGluR1 and Go-VN cDNAs appear more distantly related. Several localized regions showed a more pronounced degree of similarity, including a cysteine-rich sequence just preceding the first transmembrane domain (amino acid 206 to 260 in Go-VN1, SEO ID NO. 34), the predicted

20

25

WO 99/00422 PCT/US98/13680

transmembrane domains 2 to 7 with surrounding cytoplasmic and extracellular loops, and the relative position of 20 cysteines. The N-terminal and first transmembrane domains show little degree of homology. In mGluR and Ca2*-sensing receptors, the second intracellular loop is involved in providing specificity for G-protein coupling (Gomeza, J., et al., *J. Biol. Chem.*, 1996, 271:2199-2205), enabling different classes of mGluR receptors to activate phospholipase C or to inhibit adenylyl cyclase. In Go-VN, this domain is rich in basic residues, as expected for potential G-protein coupling, and shows closer resemblance to the class II and III mGluRs that were shown to couple to Go and Gi subunits. Overall, the six Go-VN sequences share between 42% and 75% sequence identity. Regions of Go-VN proteins downstream of transmembrane domain 2 are nearly identical in all VNO receptor sequences. In contrast, N-terminal extracellular regions and first transmembrane domains are quite divergent.

Anomalies in Go-VN cDNA Sequences: Two unusual features were observed in the sequence of some Go-VN cDNAs. In Go-VN1 (SEQ ID NO. 33) and Go-VN3 (SEQ ID NO. 37) cDNAs, stretches of open reading frame can be found in the 5' extremity of the cDNAs that generate polypeptide sequences of 310 and and 152 amino acids, respectively, which are interrupted by a frameshift in Go-VN1 and by an insertion of 500 nucleic acids in Go-VN3. The prospective receptor protein sequences indicated for Go-VN1 (SEQ ID NO. 33) and Go-VN3 (SEQ ID NO. 37) (Fig. 3) start at the next available methionin and are therefore significantly shorter than those of other receptor cDNAs.

Go-VN7 (SEQ ID NO. 45) and Go-VN13C (SEQ ID NO. 47) cDNAs show a similar deletion of 150 bp located at the exact same position in the sequence. Strikingly, the 150 bp deletion does not alter the open reading frame but generates a gap that encompasses 34 amino acids upstream of the first transmembrane domain and most of the first transmembrane domain itself.

Hydropathy analysis of Go-VN7 (SEQ ID NO. 46) and Go-VN13C (SEQ ID NO. 48) protein sequences detects only a seven to eight amino acid long hydrophobic stretch that might not be long enough to replace the deleted transmembrane domain 1 and allow the appropriate folding of the protein. Except for the 150 bp gap, sequences of Go-VN13B (SEQ ID NO. 50) and Go-VN13C (SEQ ID NO. 48) are identical. This raises the question as to whether both transcripts might originate from alternative splicing of the same gene. Alternatively, they might be transcribed from independent genes that evolved from recent duplication and deletion events.

Size f the Go-VN Family of Genes

We investigated the size of the Go-VN family of receptors by hybridizing ³²P-labeled cDNA probes prepared from regions spanning the most divergent N-terminal half of the receptor protein to rat genomic DNA. Individual probes identify two to four discrete bands under stringent conditions of hybridization and washing. Under conditions of reduced stringency, each of the individual probes now generates a unique pattern of 12 to 20 bands, providing a direct illustration of the existence of a very large family of related genes.

A direct estimate of the size of the Go-VN receptor gene family was obtained by low stringency screening of a rat genomic library. PCR amplification on genomic DNA had indicated that receptor genes are devoid of introns in the region encompassing transmembrane domains 2 to 7, enabling us to deduce directly the number of genes present in the rat genome. A mix of ³²P-labeled DNA probes prepared from the six Go-VN cDNA fragments identified 110 positive clones per haploid genome, indicating that the family of Go-VN receptors may consist of 100 genes.

15

Expression Pattern of Go-VN Receptors

The pattern of expression of the Go-VN receptor genes was examined by in situ hybridization with digoxigenin-labeled RNA antisense probes. No signal was observed after hybridizing the mix of Go-VN1 to Go-VN6 (SEQ ID NOs. 33, 35, 37, 39, 41 and 43) receptor probes to sections of muscle, testis, brain, or whole head. The adult olfactory epithelium was also consistently negative, although rare positive cells (one to three cells per section) were observed in the olfactory neuroepithelium of E19 rat embryo. In contrast, strong signals were observed when antisense receptor RNA probes were hybridized to VNO neuroepithelium. In adults, each one of the Go-VN probes detects small subsets of VNO sensory neurons. When hybridization and washing were performed at lower temperature, the number of faintly labeled neurons increased, revealing cross- hybridization to more distant receptor genes.

Under high stringency conditions, cDNA clones Go-VN1 to Go-VN6 label 1.9%, 3.6%, 6.1%, 0.4%, 3.5%, and 1.3% of the VNO sensory neurons, respectively. Under the same experimental conditions, the mix of all six Go-VN RNA probes labels 19% of the cells. This number is similar to the sum of labeled neurons detected with the six individual Go-VN probes (17%), indicating that probes representing the six receptor subfamilies recognize distinct populations of VNO sensory neurons. Spatial Distribution of Go-VN Receptor Transcripts

WO 99/00422

Positive neurons identified with each of the Go-VN probes were randomly distributed along the anteroposterior and dorso-ventral axis of the VNO neuroepithelium. Most RNA probes recognize cells that are preferentially localized in the most basal two-thirds of the neuroepithelium corresponding to the zone of Go expression. However, careful examination of adjacent cross-sections of vomeronasal neuroepithelium labeled with each of the Go-VN probes reveals a well-organized spatial distribution of receptor expression. Different receptors appear preferentially localized in radial zones that define a series of hemiconcentric rings of distinct diameters. This pattern is observed along the entire length of the VNO and is conserved in all animals analyzed. The Go-VN3 (SEQ ID NO. 37) probe, for example, recognizes a subset of neurons that are confined to the most basal third of the VNO neuroepithelium. In contrast, the Go-VN1 (SEQ ID NO. 33), Go-VN4 (SEQ ID NO. 39), and Go-VN5 (SEQ ID NO. 41) RNA probes identify cells restricted to a hemiconcentric zone immediately apical to the area of Go-VN3 expression, whereas Go-VN2 identifies cells apposed to the apical layer of supporting cells. Go-VN6 in turn is found only in sparse cells immediately apposed to the basal membrane. This is best seen in a statistical representation of Go-VN receptor localization collected from VNO sections and multiple animals that shows a striking conservation of these patterns. Thus, transcription of Go-VN cDNAs appears restricted to one of three circumscribed areas of the VNO neuroepithelium in a manner quite reminiscent of the odorant receptor gene expression in four zones of the MOE (Ressler, K., et al., Cell, 1993, 73:597-609; Vassar, R., et al., Cell, 1993, 74:309-318). Although Go-VN3 (SEQ ID NO. 37) and Go-VN6 (SEQ ID NO. 43) transcripts show a clear segregation in the most basal region of the VNO neuroepithelium, the sequence anomalies found in both transcripts leave the functionality of this area of the neuroepithelium as an open question.

25 Sexual Dimorphism in Receptor Distribution and Age-Related Changes

To identify potential sexual dimorphism in Go-VN receptor expression, we systematically hybridized each probe to sections originating from adult male and female rat VNOs. All receptors were equally distributed in males and females with the striking exception of Go-VN2 (SEQ ID NO. 35). In females, Go-VN2 appears expressed in a large and centrally located region comprising one-third of the neuroepithelium. In sharp contrast, the same probe recognizes in males a cohort of cells in the most apical side of the neuroepithelium, closely apposed to the VNO lumen, and most likely intermingled with $Gi_{2\alpha}$ VNO sensory neurons. Such a difference

in the Go-VN2 expression pattern in males and females might result from the expression of the same receptor gene in a different zone of the VNO epithelium or from a differential expression of two distinct but closely related genes of the Go-VN2 subfamily. In females, Go-VN2 generates a very intense hybridization signal to most positive neurons and a fainter staining on a second set of labeled cells. The population of faintly labeled cells was never detected in males, indicating the existence of a female-specific neuronal subpopulation expressing either a lower level of the Go-VN2 transcript or a female-specific receptor significantly different but still cross-hybridizing to the Go-VN2 probe. We followed the emergence of receptor expression and of the VNO zonal organization during development and postnatal stages preceding puberty. Go-VN receptor expression is first detected in the VNO of E14 embryos. No significant difference is observed in the onset of expression of $\text{Gi}_{2\alpha}\text{-VN}$ and Go-VN classes of receptor genes. In agreement with data of Berghard and Buck, 1996 in mouse, segregation of Gi_{2a} and Go expression in the apical and basal areas of VNO neuroepithelium, respectively, is not apparent in the embryo and in 1-week-old animals. In contrast, Gi_{2a}^+ cells appear randomly distributed in large clusters over the whole thickness of the neuroepithelium, intermingled with Go cells. At 4 weeks after birth, however, $Gi_{2\alpha}$ cells appear clearly localized in the apex of the epithelium. Similarly, in situ hybridization experiments with mixes of Go-VN and Gi_{2α}-VN receptor probes on sections of the VNOs dissected from late embryos and 1-week-old animals show that the two cell populations are still intermingled at early postnatal stages. We observed that the zonal distribution of the two families of receptors slowly emerges during sexual 20 maturation to reach the spatial distribution observed in adults. Preliminary data indicate that the sexual dimorphic expression pattern of Go-VN2 is undetectable at 6 weeks after birth. Thus, in contrast to the zones of olfactory receptor gene expression, which are already present in the olfactory epithelium at the earliest stages of receptor gene expression in the embryo (Sullivan, S., et al., Neuron, 1995, 15:779-789), the spatial organization of the VNO neuroepithelium as detected by G-protein and receptor gene expression emerges only in a late postnatal period and reaches its definitive pattern at sexual maturity.

Expression of Go-VN Receptors Is Restricted to Go+ VNO Neurons

30

The expression of some of the Go-VN receptors in neurons lining the VNO lumen in an area mainly occupied by Gi_{2a} + cells raises the obvious question as to whether the expression of this family of genes is strictly restricted to Go+ VNO neurons. Single-cell cDNA prepared from

23 individual VNO neurons was analyzed by Southern blots with probes representing the six divergent subfamilies of Go-VN receptors and was PCR amplified with degenerated primers based on conserved motifs between Go-VN receptor sequences. Both approaches confirmed that none of the 19 cell cDNAs prepared from $Gi_{2\alpha}^+$ neurons contained any sequence of the Go-VN receptor family. In contrast, all four cDNAs generated from $Gi_{2\alpha}^-$ cells contained a sequence related to the Go-VN receptors. PCR products generated with degenerated primers based on conserved motifs between Go-VN receptor sequences and obtained from the four Go+ cells were subcloned and sequenced. For each single-cell cDNA, the insert sequences from ten independent colonies were found to be identical. This set of data strongly suggests that Go-VN receptor genes are not expressed by $Gi_{2\alpha}^+$ neurons and constitutes preliminary evidence for the expression of only one Go-VN receptor gene per neuron.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims. All references disclosed herein are incorporated by reference in their entirety.

A Sequence Listing is presented below and is followed by what is claimed.

- 62 -

SEQUENCE LISTING

- (1) GENERAL INFORMATION
- (i) APPLICANT: PRESIDENT AND FELLOWS OF HARVARD COLLEGE
- (ii) TITLE OF THE INVENTION: NOVEL PHEROMONE RECEPTORS
- (iii) NUMBER OF SEQUENCES: 92
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Wolf, Greenfield & Sacks, P.C.
 - (B) STREET: 600 Atlantic Avenue
 - (C) CITY: Boston
 - (D) STATE: MA
 - (E) COUNTRY: U.S.A.
 - (F) ZIP: 02210-2211
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette
 - (B) COMPUTER: IBM Compatible
 - (C) OPERATING SYSTEM: DOS
 - (D) SOFTWARE: FastSEQ for Windows Version 2.0
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 60/051,284
 - (B) FILING DATE: 30-JUN-1997
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Plumer, Elizabeth R.
 - (B) REGISTRATION NUMBER: 36,637
 - (C) REFERENCE/DOCKET NUMBER: H0498/7074
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 617-720-3500
 - (B) TELEFAX: 617-720-2441
 - (C) TELEX:
 - (2) INFORMATION FOR SEQ ID NO:1:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3080 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 57...2606
 - (D) OTHER INFORMATION: VR1
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

																-
															Met 1	
	_			_	TTC Phe											107
					TTG Leu											155
					GAT Asp											203
CTT Leu 50	TGG Trp	AAA Lys	ACT Thr	GAT Asp	GAA Glu 55	CCT Pro	ATT Ile	GAA Glu	GAT Asp	AGT Ser 60	TTT Phe	TAT Tyr	AAT Asn	TAT Tyr	GAT Asp 65	251
TTA Leu	AGT Ser	TTT Phe	AGA Arg	ATT Ile 70	GCA Ala	GCA Ala	AGT Ser	GAA Glu	TAT Tyr 75	GAG Glu	TTT Phe	CTT Leu	CTC Leu	GTA Val 80	ATG Met	299
					GAG Glu											347
ATA Ile	ACT Thr	TTG Leu 100	ATG Met	TTC Phe	TCC Ser	TTC Phe	ATT Ile 105	GGT Gly	GGA Gly	AAC Asn	TGT Cys	CAG Gln 110	GAT Asp	TTA Leu	TTG Leu	395
					GCA Ala											443
					TAT Tyr 135											491
					ACT Thr											539
					GGA Gly											587
					CAT His											635
CAT His	GGC Gly 195	ATG Met	GTC Val	TCC Ser	TTG Leu	ATG Met 200	TTT Phe	CAC His	TTT Phe	AGA Arg	TGG Trp 205	ACT Thr	TGG Trp	ATA Ile	GGA Gly	683
					GAT Asp 215											731
					AGG Arg											779
					CAG Gln										GAT Asp	827

- 64 -

			245					250					255			
														GGT Gly		875
ATG Met	AAC Asn 275	TCT Ser	ACT Thr	CTA Leu	GAA Glu	GCA Ala 280	AGC Ser	TTT Phe	AGA Arg	AGA Arg	TGG Trp 285	GAA Glu	GAG Glu	TTA Leu	GGT Gly	923
GCT Ala 290	CGG Arg	AGA Arg	ATC Ile	TGG Trp	ATC Ile 295	ACA Thr	ACC Thr	TCA Ser	CAA Gln	TGG Trp 300	GAT Asp	GTC Val	ATC Ile	ACA Thr	AAT Asn 305	971
AAA Lys	AAA Lys	GAC Asp	TTC Phe	ACC Thr 310	CTT Leu	AAT Asn	CTC Leu	TTC Phe	CAT His 315	GGG Gly	ATC Ile	ATC Ile	ACT Thr	TTT Phe 320	GAA Glu	1019
														ACA Thr		1067
AAC Asn	ACT Thr	GCC Ala 340	AAA Lys	TAC Tyr	CCA Pro	GTA Val	GAT Asp 345	ATT Ile	TCT Ser	CAT His	ACT Thr	ATA Ile 350	TTG Leu	GAG Glu	TGG Trp	1115
AAT Asn	TAT Tyr 355	TTT Phe	AAT Asn	TGT Cys	TCA Ser	ATA Ile 360	TCT Ser	AAG Lys	AAC Asn	AGC Ser	ATT Ile 365	AGA Arg	ATG Met	CAT His	CAT His	1163
ATT Ile 370	ACA Thr	TTC Phe	AAC Asn	AAC Asn	ACC Thr 375	TTG Leu	GAA Glu	TGG Trp	ACA Thr	TCA Ser 380	CTG Leu	CAC His	AAC Asn	TAT Tyr	GAT Asp 385	1211
GTG Val	GCG Ala	ATG Met	AGT Ser	GAT Asp 390	GAA Glu	GGT Gly	TAC Tyr	AAT Asn	TTG Leu 395	TAC Tyr	AAT Asn	GCT Ala	GTT Val	TAT Tyr 400	GCT Ala	1259
														TCT Ser		1307
														GTG Val		1355
														CTG Leu		1403
AAC Asn 450	ATG Met	AAG Lys	CAT His	AGG Arg	GAA Glu 455	TAA naA	CAG Gln	TGT Cys	ACA Thr	GAG Glu 460	TAT Tyr	GAT Asp	ATT Ile	TTC Phe	ATC Ile 465	1451
ATT Ile	TGG Trp	AAT Asn	TTT Phe	CCA Pro 470	CAA Gln	GGC Gly	CTT Leu	GGA Gly	TTA Leu 475	AAA Lys	GTG Val	AAA Lys	ATA Ile	GGA Gly 480	AGC Ser	1499
														GAT Asp		1547
TTG Leu	GAA Glu	TGG Trp 500	GCC Ala	AAG Lys	GGA Gly	GGA Gly	ACA Thr 505	TCA Ser	CCT Pro	CAG Gln	GTT Val	CCC Pro 510	TCC Ser	TCC Ser	GTG Val	1595

																•
			GCA Ala													1643
			TGC Cys													1691
TCC Ser	AAC Asn	GAA Glu	ACA Thr	GAT Asp 550	ATG Met	GAA Glu	CAG Gln	TGT Cys	GTG Val 555	AGG Arg	TGT Cys	CCA Pro	GAT Asp	GAT Asp 560	AAG Lys	1739
TAT Tyr	GCC Ala	AAC Asn	ATA Ile 565	GAG Glu	CAA Gln	ACC Thr	CAC His	TGC Cys 570	CTC Leu	TCA Ser	AGA Arg	GCT Ala	GTA Val 575	TCA Ser	TTT Phe	1787
CTG Leu	GCT Ala	TAT Tyr 580	GAA Glu	GAT Asp	TCA Ser	TTG Leu	GGG Gly 585	ATG Met	GCT Ala	CTA Leu	GGC Gly	TGC Cys 590	ATG Met	GCA Ala	CTG Leu	1835
TCC Ser	TTC Phe 595	TCA Ser	GCC Ala	ATC Ile	ACA Thr	ATT Ile 600	CTA Leu	ATC Ile	CTC Leu	GTC Val	ACA Thr 605	TTT Phe	GTG Val	AAG Lys	TAC Tyr	1883
AAA Lys 610	GAT Asp	ACT Thr	CCC Pro	ACT Thr	GTG Val 615	AAG Lys	GCC Ala	AAT Asn	AAC Asn	CGC Arg 620	ATT Ile	CTC Leu	AGC Ser	TAC Tyr	ATC Ile 625	1931
CTG Leu	CTC Leu	ATC Ile	TCT Ser	CTC Leu 630	GTC Val	TTC Phe	TGC Cys	TTT Phe	CTC Leu 635	TGC Cys	TCC Ser	CTG Leu	CTC Leu	TTC Phe 640	ATT Ile	1979
			GAC Asp 645													2027
			ACT Thr													2075
			GCT Ala													2123
			ACA Thr													2171
			GTT Val													2219
ATT Ile	GAC Asp	AGA Arg	GAC Asp 725	ATA Ile	CAA Gln	TCT Ser	GAG Glu	CAT His 730	GGG Gly	AAG Lys	ATT Ile	GTC Val	ATT Ile 735	CTT Leu	TGC Cys	2267
			TCA Ser													2315
TCC Ser	TTG Leu 755	GCT Ala	CTG Leu	GGG Gly	AGC Ser	TTC Phe 760	ACG Thr	TTG Leu	GCT Ala	TTC Phe	CTG Leu 765	GCT Ala	AGG Arg	AAC Asn	CTT Leu	2363
CCT	GAC	ACA	TTC	AAT	GAA	GCC	AAG	TTC	CTA	ACT	TTC	AGC	ATG	CTG	GTG .	2411

Pro 770	Asp	Thr	Phe	Asn	Glu 775	Ala	Lys	Phe	Leu	Thr 780	Phe	Ser	Met	Leu	Val 785	
														ACC Thr 800		2459
_														TCT Ser		2507
		-												ATT Ile	_	2555
						-							-,	TTG Leu		2603
TAT Tyr 850	TGA	AACTT	TTC 3	ATGG7	ratg <i>i</i>	LA AA	ATGTT	'AGA'	GAT	ratt(CAAC	TTAT	rctt/	ATT (TTCAT	2662
CTT	ATA	AAA C	CAG	ract:	C A	CAT	AATA	XAA A	LAAT	AGTA	ATAT	CACAC	AT :	TATI	CTTAC	2722
									-						GCTAC	2782
															TATGAG	2842
															TAAGAA	2902
															CTTTCA AGGTAG	2962 3022
														CGGC		3022
				1.		1					JACK					2000

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 850 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Lys Gln Leu Cys Ala Phe Thr Ile Ser Leu Leu Phe Leu Lys Phe 5 10 15 Ser, Leu Ile Leu Cys Cys Leu Thr Glu Pro Ser Cys Phe Trp Arg Ile 25 Arg Asn Ser Glu Asp Ser Asp Gly Asp Leu Gln Arg Glu Cys His Phe Tyr Leu Trp Lys Thr Asp Glu Pro Ile Glu Asp Ser Phe Tyr Asn Tyr 55 60 Asp Leu Ser Phe Arg Ile Ala Ala Ser Glu Tyr Glu Phe Leu Leu Val 75 70 Met Phe Phe Ala Ile Asp Glu Ile Asn Arg Asn Pro Tyr Leu Leu Pro 85 90 Asn Ile Thr Leu Met Phe Ser Phe Ile Gly Gly Asn Cys Gln Asp Leu 100 105 110 Leu Arg Val Met Asp Gln Ala Tyr Thr Gln Ile Asn Gly His Met Asn 120 115 125 Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Ala Ile Gly Leu 130 135 140 Thr Gly Pro Ser Trp Lys Thr Ser Leu Lys Leu Ala Met His Ser Ser 155 150 Met Pro Leu Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His.

Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu Ser His Gly Met Val Ser Leu Met Phe His Phe Arg Trp Thr Trp Ile Gly Leu Val Ile Ser Asp Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr Asp Lys His Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly Glu Met Asn Ser Thr Leu Glu Ala Ser Phe Arg Arg Trp Glu Glu Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln Trp Asp Val Ile Thr Asn Lys Lys Asp Phe Thr Leu Asn Leu Phe His Gly Ile Ile Thr Phe Glu His His Arg Phe Glu Ile Pro Lys Leu Asn Lys Phe Met Gln Thr Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser His Thr Ile Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ile Arg Met His His Ile Thr Phe Asn Asn Thr Leu Glu Trp Thr Ser Leu His Asn Tyr Asp Val Ala Met Ser Asp Glu Gly Tyr Asn Leu Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu Tyr Ile Phe Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Tyr Phe Thr Ala Cys Gln Gln Val Ser Ser Leu Met Lys Thr Arg Val Phe Thr Asn Pro Val Gly Glu Leu Val Asn Met Lys His Arg Glu Asn Gln Cys Thr Glu Tyr Asp Ile Phe Ile Ile Trp Asn Phe Pro Gln Gly Leu Gly Leu Lys Val Lys Ile Gly Ser Tyr Leu Pro Cys Phe Pro Gln Arg Gln Lys Leu His Ile Ser Asp Asp Leu Glu Trp Ala Lys Gly Gly Thr Ser Pro Gln Val Pro Ser Ser Val Cys Ser Val Ala Cys Thr Ala Gly Phe Arg Lys Ile Tyr Gln Lys Glu Thr Ala Asp Cys Cys Phe Asp Cys Val Gln Cys Pro Glu Asn Glu Ile Ser Asn Glu Thr Asp Met Glu Gln Cys Val Arg Cys Pro Asp Asp Lys Tyr Ala Asn Ile Glu Gln Thr His Cys Leu Ser Arg Ala Val Ser Phe Leu Ala Tyr Glu Asp Ser Leu Gly Met Ala Leu Gly Cys Met Ala Leu Ser Phe Ser Ala Ile Thr Ile Leu Ile Leu Val Thr Phe Val Lys Tyr Lys Asp Thr Pro Thr Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Ile Leu Leu Ile Ser Leu Val Phe Cys Phe Leu Cys Ser Leu Leu Phe Ile Gly Pro Pro Asp Gln Val Thr Cys Ile Phe Gln Gln Thr Thr Phe Gly Val Leu Phe Thr Val Ser Val Ser Thr Val Leu Ala Lys Thr Ile Thr Val Val Met Ala Phe Lys Leu Thr Thr Pro Gly Arg Arg Met Arg

- 68 -

Gly Met Met Met Thr Gly Ala Pro Lys Leu Val Ile Pro Ile Cys Thr 695 700 Leu Ile Gln Leu Val Leu Cys Gly Ile Trp Leu Val Thr Ser Pro Pro 715 705 710 Phe Ile Asp Arg Asp Ile Gln Ser Glu His Gly Lys Ile Val Ile Leu 725 730 Cys Asn Lys Gly Ser Val Ile Ala Phe His Val Val Leu Gly Tyr Leu 740 745 Gly Ser Leu Ala Leu Gly Ser Phe Thr Leu Ala Phe Leu Ala Arg Asn 760 765 Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu 775 780 770 Val Phe Cys Ser Val Trp Ile Thr Phe Leu Pro Val Tyr His Ser Thr 790 795 785 Arg Gly Arg Val Met Val Val Val Glu Val Phe Ser Ile Leu Ala Ser 805 810 815 Ser Ala Gly Leu Leu Met Cys Ile Phe Val Pro Lys Cys Tyr Val Ile 825 830 820 Leu Ile Arg Pro Asp Ser Asn Phe Ile Lys Asn His Lys Gly Lys Leu 840 845 Leu Tyr 850

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2961 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 86...2509
 - (D) OTHER INFORMATION: VR2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

(iii)																
AGACACATCG GTGCAACTGT GTGTGTGATG TTTTTCTGCA TCAGAAACGG ATTTCACAGC 6														60		
AGC	CCAT	CT C	'AGA'	CCTA	AG CZ	AGAC	ATG	AAG	CAG	CTC	TGC	ACT	TTC	ACT	ATT	112
							Met 1	ГÀЗ	Gln	Leu	Cys 5	Thr	Phe	Thr	Ile	
TCA	TTG	TTG	TTT	CTG	AAG	TTT	TCT	CTC	ATC	TTG	TGC	TGT	TGG	AGT	GAA	160
Ser	Leu	Leu	Phe	Leu	Lys	Phe	Ser	Leu	Ile	Leu	Сув	Cys	Trp	Ser	Glu	
10					15					20	-				25	
					AGG											208
Pro	Ser	Cys	Phe	Trp 30	Arg	Ile	Lys	Lys	Ser 35	Glu	Asp	Asn	Asp	Gly 40	Asp	
מידים	CAA	AGG	GAG	ጥርጥ	CAT	Jahah	TAC	CTT	TGG	AAA	ACT	GAT	GAA	CCT	ATT	256
					His											
		_	45				•	50	-	•		-	55			
GAA	GAT	AGT	TTT	TAT	AAT	TAT	GAT	TTA	AGT	TTT	AGA	ATT	GCA	GGA	AGT	304
Glu	Asp	Ser 60	Phe	Tyr	Asn	Tyr	Asp 65	Leu	Ser	Phe	Arg	Ile 70	Ala	Gly	Ser	
																252
					CTG											352
Glu	Tyr 75	Glu	Leu	Leu	Leu	Val 80	Met	Phe	Phe	Ala	Thr 85	Asp	Glu	тте	Asn	

																-
														ATC Ile		400
														TAT Tyr 120		448
														TTA Leu		496
														TCC Ser		544
														CCA Pro		592
														CAG Gln		640
														ATG Met 200		688
														GAT Asp		736
														CAT His		784
														ATA Ile		832
														TCA Ser	GCA Ala 265	880
		Val	Ile		Tyr	Gly	Asp	Met	Asn	Ser				GCA Ala 280		928
														ACA Thr		976
														AAT Asn		1024
														CCT Pro	AAA Lys	1072
	Arg													GTA Val	GAT Asp 345	1120
ATT	TCT	CAT	ACT	ATT	TTG	GAG	TGG	AAT	TAT	TTT	AAT	TGT	TCA	ATC	TCT	. 1168

																_
·11	e Ser	His	Thr	11e 350	Leu	Glu	Trp	Asn	Tyr 355	Phe	Asn	Сув	Ser	Ile 360	Ser	
	G AAC s Asn															1216
	G ACA p Thr											_				1264
AA As	T TTG n Leu 395	TAT Tyr	AAT Asn	GCT Ala	GTT Val	TAT Tyr 400	GCT Ala	GTG Val	GCC Ala	CAC His	ACC Thr 405	TAC Tyr	CAT His	GAA Glu	TAC Tyr	1312
AT Il 41	T CTT e Leu 0	CAA Gln	CAA Gln	GTA Val	GAG Glu 415	TCT Ser	CAG Gln	AAA Lys	AAG Lys	GCA Ala 420	AAA Lys	CCC Pro	AAA Lys	AGA Arg	TAT Tyr 425	1360
	C ACT e Thr															1408
	G AAC t Asn															1456
	T ACA s Thr															1504
	A TTA y Leu 475	Lys														1552
	A CAA n Gln 0															1600
	A GTG r Val															1648
	T TTA n Leu															1696
	T GAA r Glu															1744
	G GCC r Ala 555															1792
	T CCC r Pro 0															1840
	C TCT e Ser															1888
	C GAC o Asp														TTG Leu .	1936

- 71 -

	605	610	615	
TTC ACT GTG Phe Thr Val 620	TCT GTT TCT ACA G Ser Val Ser Thr Va	TG TTG GCC AAA A al Leu Ala Lys T 25	CA ATA ACT GTG GT hr lle Thr Val Va 630	C 1984
ATG GCT TTC Met Ala Phe 635	AAG CTC ACT ACT CO Lys Leu Thr Thr P: 640	ro Gly Arg Arg M	TG AGA GGG ATG AT et Arg Gly Met Me 45	G 2032
ATG ACA GGG Met Thr Gly 650	GCA CCT AAG TTG G Ala Pro Lys Leu V 655	TC ATT CCC ATT TO al Ile Pro Ile C 660	GT ACC CTG ATC CA ys Thr Leu Ile Gl 66	n
CTT GTT CTC Leu Val Leu	TGT GGA ATC TGG T Cys Gly Ile Trp Lo 670	TG GTC ACA TCT C eu Val Thr Ser P 675	CT CCC TTT ATT GA ro Pro Phe Ile As 680	C 2128
AGA GAT ATA Arg Asp Ile	CAA TCT GAA CAT GG Gln Ser Glu His G 685	GG AAG ATT GTC A' ly Lys Ile Val I 690	TT CTT TGC AAT AA le Leu Cys Asn Ly 695	A 2176
GGC TCT GTC Gly Ser Val 700	GTT GCC TTC CAC GY Val Ala Phe His Va	TC GTC CTG GGA T al Val Leu Gly T 05	AC TTG GGC TCC TT yr Leu Gly Ser Le 710	rg 2224 nu
GCT CTG GGG Ala Leu Gly 715	AGC TTC ACT TTG GG Ser Phe Thr Leu A 720	la Phe Leu Ala A	GG AAC CTT CCT GA rg Asn Leu Pro As 25	C 2272
	GAA GCC AAG TTC C Glu Ala Lys Phe Lo 735			rs
	ATC ACC TTC CTC CO Ile Thr Phe Leu Po 750			
	GTT GTG GAG GTT T Val Val Glu Val Pl 765			
	TGT ATC TTT GTC CC Cys Ile Phe Val P:			
CCA GAT TCA Pro Asp Ser 795	AAT TTT ATA CAG AAASn Phe Ile Gln Aa	sn His Lys Gly L	AA TTG CTT TAT TG ys Leu Leu Tyr 05	AAA 2514
AGCAGTACTT AGCAAACATG GATCTGTGGT CTGTCTTTGA CATACACAAT TACTTCCAAG	ATGAAAATGT TAGATGA' CATCATATAA AAAATAA AATATGTTGA GAACTGG TTTGTGTTTA AGCCATG' ACAGCGCCAC CTCTAGG GGACATGAAG CCAGTAA' TTCATGCCTT GACTTTA' TCCTCACAAA AAAAAAA	AGT AATATACAGA T GAT TCTCAATTGA G TAC TTAATTAATG A CAT GCTGTCCTTG A TCA ACATTATTCC A TTC AATGTTCTAT G	TTATACTTA CAAACTG GAATGGCTA CCAATAT TTAACATGA GGTTACC GTTATAAGA AAGGGTA CTTGCTTTC ATGGAGT	GAC 2634 TTT 2694 CTA 2754 CTG 2814 TCT 2874

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 808 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein(v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Lys Gln Leu Cys Thr Phe Thr Ile Ser Leu Leu Phe Leu Lys Phe Ser Leu Ile Leu Cys Cys Trp Ser Glu Pro Ser Cys Phe Trp Arg Ile Lys Lys Ser Glu Asp Asn Asp Gly Asp Leu Gln Arg Glu Cys His Phe Tyr Leu Trp Lys Thr Asp Glu Pro Ile Glu Asp Ser Phe Tyr Asn Tyr Asp Leu Ser Phe Arg Ile Ala Gly Ser Glu Tyr Glu Leu Leu Leu Val Met Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu Leu Pro Asn Met Ser Leu Met Phe Ser Ile Ile Gly Gly Asn Cys His Asp Leu Leu Arg Ser Leu Asp Gln Glu Tyr Ala Gln Ile Asp Gly His Met Asn Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Ala Thr Gly Leu Thr Gly Pro Ser Trp Lys Thr Ser Leu Lys Leu Ala Met His Ser Ser Met Pro Leu Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu Ser His Gly Met Val Ser Leu Met Phe His Phe Arg Trp Thr Trp Ile Gly Leu Val Ile Ser Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr Asp Thr Gln Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly Asp Met Asn Ser Thr Leu Glu Ala Ser Phe Arg Arg Trp Glu Glu Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr Thr Gln Trp Asp Val Ile Thr Asn Lys Lys Asp Phe Thr Leu Asn Leu Phe His Gly Thr Ile Thr Phe Ala His His Lys Asp Glu Ile Pro Lys Phe Arg Asn Phe Met Gln Thr Lys Lys Thr Ala Lys Tyr Leu Val Asp Ile Ser His Thr Ile Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ser Lys Met Gly His Phe Thr Phe Asn Asn Thr Leu Gln Trp Thr Ala Leu His Asn Tyr Asp Met Ala Leu Ser Asp Glu Gly Tyr Asn Leu Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu Tyr Ile Leu Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Tyr Phe Thr Ala Cys Gln Gln Val Ser Ser Leu Met Lys Thr Arg Val Phe Met Asn Pro Val Gly Glu Leu Val Asn Met Lys His Arg Glu Asn Gln Cys Thr Glu Tyr Asp Ile Phe

48

Ile Ile Trp Asn Phe Pro Gln Gly Leu Gly Leu Lys Val Lys Val Gly 470 475 Ser Tyr Leu Pro Cys Phe Pro Lys Ser Gln Gln Leu His Ile Ala Asp 485 490 Asp Leu Glu Trp Ala Met Gly Gly Thr Ser Val Asp Met Glu Gln Cys 500 505 510 Val Arg Cys Pro Asp Asn Lys Tyr Ala Asn Leu Glu Gln Thr His Cys 520 515 525 Leu Gln Arg Thr Val Ser Phe Leu Ala Tyr Glu Asp Pro Leu Gly Met 535 540 Ala Leu Gly Cys Met Ala Leu Ser Phe Ser Ala Ile Thr Ile Leu Val 550 555 Leu Val Thr Phe Val Lys Tyr Lys Asp Thr Pro Ile Val Lys Ala Asn 565 570 575 Asn Arg Ile Leu Ser Tyr Ile Leu Leu Ile Ser Leu Val Phe Cys Phe 580 585 590 Leu Cys Ser Leu Leu Phe Ile Gly His Pro Asp Gln Val Thr Cys Ile 595 600 605 Leu Gln Gln Thr Thr Phe Gly Val Leu Phe Thr Val Ser Val Ser Thr 615 620 Val Leu Ala Lys Thr Ile Thr Val Val Met Ala Phe Lys Leu Thr Thr 630 635 Pro Gly Arg Arg Met Arg Gly Met Met Thr Gly Ala Pro Lys Leu 645 650 Val Ile Pro Ile Cys Thr Leu Ile Gln Leu Val Leu Cys Gly Ile Trp 665 660 670 Leu Val Thr Ser Pro Pro Phe Ile Asp Arg Asp Ile Gln Ser Glu His 680 675 685 Gly Lys Ile Val Ile Leu Cys Asn Lys Gly Ser Val Val Ala Phe His 690 700 695 Val Val Leu Gly Tyr Leu Gly Ser Leu Ala Leu Gly Ser Phe Thr Leu 710 715 Ala Phe Leu Ala Arg Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe 725 730 735 Leu Thr Phe Ser Met Leu Val Phe Cys Ser Val Trp Ile Thr Phe Leu 740 745 750 Pro Val Tyr His Ser Thr Arg Gly Lys Val Met Val Val Val Glu Val 765 755 760 Phe Ser Ile Leu Ala Ser Ser Ala Gly Leu Leu Met Cys Ile Phe Val 770 775 780 Pro Lys Cys Tyr Val Ile Leu Ile Arg Pro Asp Ser Asn Phe Ile Gln 790 795 Asn His Lys Gly Lys Leu Leu Tyr 805

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2907 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 1...2409
 - (D) OTHER INFORMATION: VR3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CAT TTT TAC CTT GGG GCA GTT GAT AAA CCA ATT GAA GAT AAT TTT TAT His Phe Tyr Leu Gly Ala Val Asp Lys Pro Ile Glu Asp Asn Phe Tyr

WO 99/00422 - 74 -

					•					-
1		5			10			15		
		AAG Lys								96
		TTT Phe								144
		ACT Thr								192
		GGT Gly								240
		AAT Asn 85								288
		CCA Pro								336
		CTG Leu								384
		CTG Leu								432
		GGC Gly								480
		GTC Val 165								528
	 	 GAA Glu	 							576
		CCA Pro								624
		CAA Gln								672
		AAC Asn								720
		CGG Arg 245				Thr				768
		AAA Lys							_	816

																-
	TTT Phe															864
	ACA Thr 290															912
	GAG Glu															960
	GAT Asp															1008
	TAT Tyr															1056
	TAT Tyr															1104
	TCT Ser 370															1152
	GTG Val															1200
	CTG Leu															1248
	TTC Phe															1296
	GGA Gly														_	1344
	GAT Asp 450			Glu	Trp		Met			Thr						1392
	GTG Val														CAG Gln 480	1440
	GAA Glu															1488
	GTT Val															1536
	AAG Lys															1584
TCA	TTT	CTG	GCT	TAT	GAA	GAT	CCA	TTG	GGG	ATA	GCT	CTA	GGC	TGC	ATA ·	1632

Ser	Phe 530	Leu	Ala	Tyr	Glu	Asp 535	Pro	Leu	Gly	Ile	Ala 540	Leu	Gly	Cys	Ile	
	CTG Leu															1680
	TAC Tyr															1728
	ATC Ile															1776
	ATT Ile															1824
	GGA Gly 610															1872
	ACT Thr															1920
	GAG Glu															1968
	CTA Leu															2016
	TTT Phe															2064
	TGC Cys 690															2112
	GGC Gly															2160
	CTT Leu															2208
	GTG Val															2256
	AGG Arg		Lys													2304
	AGT Ser 770						Cys					Lys				2352
															AAA Lys .	2400

- 77 -

785 790 795 800

TTT CGT TAT TGAAATATTC ATACTATGAA AATGTTAGAT TATACTCAAC ATATTTTTC 2458 Phe Arg Tyr

TTTGTCTTAA CAAAAGTAGT ACTTAATCTT ATAAAAATTT AAATAATATA CAAATTTGAA 2518
CTTACAAACA GGACAGAACT GTCTATTGTA ATACCAATTA CAAAACTTTG GTGAAAAATG 2578
GTCTCATTCA TAAGGACACA ATTCTGAAGA TATTGAGAAC CAGGAATCTC AACTGCGGAA 2638
ACGCTACCAT CATCCTGACC TGTGGTTTTG TGTGTAAAGC ATGAACTTAA TTAATGATTA 2698
ATATAAAGGTG ACCATACTGA CTGTGAACAC TACCATCTCT GGGCAAGTTG TTCTTGTAGT 2758
TGTAAGAAAA AGCTCTGAAG ACAACATGGA AGTAAAGCCA GTAATCACCA TTATCCCTCA 2818
TGCTTTCATG GAGTGGCTGC ATCCAATTTC ATGCCTTGGC TTCATTCAAT ATACTGTGAC 2907

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 803 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

His Phe Tyr Leu Gly Ala Val Asp Lys Pro Ile Glu Asp Asn Phe Tyr 10 Asn Ser Leu Leu Lys Phe Arg Ile Ala Ala Ser Glu Tyr Glu Phe Leu 20 25 Leu Val Met Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu 40 Leu Pro Asn Ile Thr Leu Met Phe Ser Ile Ile Gly Gly Asn Cys His 55 Asp Leu Leu Arg Gly Leu Asp Gln Ala Tyr Thr Gln Ile Asn Gly His 70 75 Met Asn Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Ala Ile 90 Gly Leu Thr Gly Pro Ser Trp Lys Thr Ser Leu Asn Leu Ala Met His 105 Ser Ser Met Pro Leu Val Phe Phe Gly Ser Phe Asn Pro Asn Leu His 120 125 Asp His Asp Arg Leu His His Val His Gln Val Ala Thr Lys Asp Thr 135 140 His Leu Ser His Gly Ile Val Ser Leu Met Phe His Phe Arg Trp Thr 150 155 Trp Ile Gly Leu Val Ile Ser Asp Asp Asp Lys Gly Ile Gln Phe Leu 170 165 Ser Asp Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe 180 185 190 Val Asn Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr 195 200 205 Ile Tyr Asp Lys Gln Ile Met Thr Ser Leu Ala Lys Val Val Ile Ile 215 210 220 Tyr Gly Glu Met Asn Ser Thr Leu Glu Val Ser Phe Arg Arg Trp Glu 230 235 240 Asn Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln Trp Asp Val 245 250 Ile Thr Asn Lys Lys Glu Phe Thr Leu Asn Leu Phe His Gly Thr Ile 265 Thr Phe Ala His Arg Arg Phe Glu Ile Pro Lys Phe Lys Lys Phe Met 280 Gln Thr Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser His Thr Ile .

Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ser Lys Met Asp His Ile Thr Phe Asn Asn Thr Leu Glu Trp Thr Ala Leu His Asn Tyr Asp Met Val Met Ser Asp Glu Gly Tyr Asn Leu Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu His Ile Phe Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Phe Phe Thr Val Cys Gln Gln Val Ser Ser Leu Met Lys Thr Arg Val Phe Thr Asn Pro Val Gly Glu Leu Val Asn Met Lys His Arg Glu Asn Gln Cys Thr Glu Tyr Asp Ile Phe Leu Ile Trp Asn Phe Pro Gln Gly Leu Gly Leu Lys Val Lys Ile Gly Ser Tyr Leu Pro Cys Phe Pro Gln Arg Gln Glu Leu His Ile Ser Asp Asp Leu Glu Trp Ala Met Gly Gly Thr Ser Val Val Pro Ser Ser Val Cys Ser Val Ala Cys Thr Ala Gly Phe Arg Lys Ile His Gln Lys Glu Thr Ala Asp Cys Cys Phe Asp Cys Val Gln Cys Pro Glu Asn Glu Val Ser Asn Glu Thr Asp Met Glu Gln Cys Val Lys Cys Pro Tyr Asp Lys Tyr Ala Asn Ile Glu Lys Thr His Cys Leu Ser Arg Ala Val Ser Phe Leu Ala Tyr Glu Asp Pro Leu Gly Ile Ala Leu Gly Cys Ile Ala Leu Ser Phe Ser Ala Ile Thr Ile Leu Val Leu Ile Thr Phe Leu Lys Tyr Lys Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Ile Leu Leu Ile Ser Leu Val Phe Cys Phe Leu Cys Ser Leu Leu Phe Ile Gly His Pro Asn Gln Val Ser Cys Val Leu Gln Gln Thr Thr Phe Gly Val Phe Phe Thr Val Ser Val Ser Thr Val Leu Ala Lys Thr Ile Thr Val Val Met Ala Phe Lys Leu Thr Thr Pro Gly Arg Arg Met Arg Glu Met Leu Val Thr Gly Ala Pro Lys Leu Val Ile Pro Ile Cys Thr Leu Ile Gln Phe Val Leu Cys Gly Ile Trp Leu Ile Thr Ser Pro Pro Phe Ile Asp Arg Asp Ile Gln Ser Glu His Gly Lys Ile Val Ile Leu Cys Asn Lys Gly Ser Val Ile Ala Phe His Val Val Leu Gly Tyr Leu Gly Ser Leu Ala Leu Gly Ser Phe Thr Leu Ala Phe Leu Ala Arg Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe Cys Ser Val Trp Ile Thr Phe Leu Pro Val Tyr His Ser Thr Arg Gly Lys Val Met Val Val Val Glu Val Phe Ser Ile Leu Ala Ser Ser Ala Gly Leu Leu Met Cys Ile Phe Val Pro Lys Cys Tyr Val Ile Leu Val Arg Pro Asp Ser Asn Phe Ile Arg Lys Tyr Lys Asp Lys Phe Arg Tyr

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3625 base pairs
 (B) TYPE: nucleic acid

 - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence (B) LOCATION: 117...2672

 - (D) OTHER INFORMATION: VR4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGAATATGCA ATAAACCTCA CATTTGCACA AAGAAATAAA AGCTGGTAGA AATCTGATGT GCTGATATGC ATGGCACTTC ACAATCCGCA CTGCCCAGGT TTAAGGCAGG AAAAAG ATG Met 1 TTC ATT TTC ATG GGA GTC TTC TTC CTA CTT AAT ATT ACA CTT CTC ATG														
TTC ATT TTC ATG GGA Phe Ile Phe Met Gly 5	GTC TTC TTC CTA Val Phe Phe Lev 10	A CTT AAT AT u Leu Asn Il	TT ACA CTT CTC le Thr Leu Leu 15	ATG 167 Met										
GCC AAT TTC ATT GAT Ala Asn Phe Ile Asp 20														
ATA ACG GAT GAA TAT Ile Thr Asp Glu Tyr 35			ne Ile Leu Ala											
GTT CAG ACA CCC ATT Val Gln Thr Pro Ile 50			nr Thr Leu Asn											
CTA AAA ACT ACT AAA Leu Lys Thr Thr Lys 70	AAC CAC AAA TAT Asn His Lys Tyr	r GCT TTG GC r Ala Leu Al 75	CA TTG GTG TTT la Leu Val Phe 80	GCA 359 Ala										
ATG GAT GAA ATC AAC Met Asp Glu Ile Asn 85														
ATT ATC AGA TAC TCT Ile Ile Arg Tyr Ser 100														
ACA CCA TAT TTA TTT Thr Pro Tyr Leu Phe 115	CAT AGA AAA AAG His Arg Lys Lys 120	G CAA AGC CC G Gln Ser Pr 12	ro Ile Pro Asn	TAT 503 Tyr										
TTC TGT AAT GAA GAG Phe Cys Asn Glu Glu 130			eu Ser Gly Pro											
TGG GAT GAA TCT TTA Trp Asp Glu Ser Leu 150														
CCA CGT ATC CTT CAG Pro Arg Ile Leu Gln	CTT TCC TAT GGA Leu Ser Tyr Gly	A TCT TTC AG y Ser Phe Se	GT TCC ATC TTC er Ser Ile Phe	AGT 647 Ser										

WO 99/00422 PCT/US98/13680 - 80 -

16	65	170	175	
	ln Tyr Pro Tyr		G GCC CCA AAA GAC t Ala Pro Lys Asp 190	
			T TAT TTG AAA TGG u Tyr Leu Lys Trp 205	
			A GGA AAC CAA TTT n Gly Asn Gln Phe 0	
			A ATT TGC TTT GCC u lle Cys Phe Ala 240	
Val Lys Met I			T CCA CAA AAA ACT e Pro Gln Lys Thr 255	
	ys Gln Ile Val		A AAT GTT ATT ATC r Asn Val Ile Ile 270	
			C TTC AGA ATG TGG e Phe Arg Met Trp 285	
			A AAA CAA TTG AAT r Lys Gln Leu Asn 0	
			A TTC TAT GGA TCA r Phe Tyr Gly Ser 320	
Thr Phe Leu Pr			C TTT AAA AAT TTT y Phe Lys Asn Phe 335	
			A TGT CTA GTA ATG u Cys Leu Val Met 350	
			A TCT AAT TGT AAA a Ser Asn Cys Lys 365	
			T TGG CTA ATG GAA p Trp Leu Met Glu 0	
			T AAC ATA TAT AAT s Asn Ile Tyr Asn 400	
Val His Ala I			G AAT CTG CAA CAG t Asn Leu Gln Gln 415	
			C AGT TCT CAC TGC a Ser Ser His Cys 430	

	_				CTA Leu											1463
					AAG Lys 455											1511
					AAT Asn											1559
					CCA Pro											1607
					GAG Glu											1655
TCT Ser	GTG Val 515	TGC Cys	AGT Ser	GCA Ala	GAT Asp	TGT Cys 520	AGT Ser	CCT Pro	GGA Gly	TTC Phe	AGA Arg 525	AGA Arg	TTA Leu	TGG Trp	AAG Lys	1703
					TGC Cys 535											1751
					ACA Thr											1799
					ACA Thr											1847
					GAA Glu											1895
					GCA Ala											1943
	_				CCT Pro 615											1991
					TCA Ser											2039
					AAC Asn											2087
					ACT Thr											2135
					GCT Ala											2183
AGA	TAC	TTC	CTT	GTA	TCA	GGG	ACA	CTA	AAC	TAC	ATT	ATT	CCT	ATA	TGT.	2231

- 82 -

																_
Arg 690	Tyr	Phe	Leu	Val	Ser 695	Gly	Thr	Leu	Asn	Tyr 700	Ile	Ile	Pro	Ile	Cys 705	
			CAA Gln													2279
			GAT Asp 725													2327
			AAG Lys													2375
			CTG Leu													2423
			GAT Asp													2471
			TGC Cys													2519
			AAA Lys 805													2567
			GGG Gly										Ile			2615
			AGA Arg													2663
	TAT Tyr		TGA	ACAAJ	ATA :	ATT?	GAA'	rt C	rgtc <i>i</i>	AAT	TAJ	AAGT:	rggt	ACA!	TAACCA	2721
GTG. TCA' CTTC CAG' AGA' AAG' GAC' GTG AACC GATC CAC	ATAAAATTAAATTAAACCAAAACCAAAACCAAAACCAAAAAA	AAG (CTT) TTG I ATC (CTT) ATC (TTT) ATC (TTT) ATC (TTT) ACA I ACA I ACA (ACA (ACA (ACA (ACA (ACA (ACA (ACA	GAAGT FCTT(AATT) CACC/ FACC/ CAGA/ FTCT FCAA/ FCGG/ CCCA(FCCC/ FCCA(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(FCAT(F	TATCA	AT ACTOR OF THE AC	CTAC CTAC CTAC CTAC CTAC CAC CAC CAC CAC	CTGAL AGAGA	A CTTA ACTA ACTA ATO GAO T GAO G G G G	CCCTCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	TACA CTCT CCTA CCTA CACA AGAG AATA AATG GGAG CTAA GCCT TTGG TTAG	GTGT CCAA GGAC GACT ATCT ATCT GGTC CCAC GGTC GAAC ATGT	CACAL AAAA AAAA AAAC AAAA CAAAA AAAA AA	TAA I TTA (AAC (CAG (AATC: CAAT: STTG! SGTT! ATAA: AGAA! CAGGG ATTC: TACA(CAGTG SCAT: STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(STCA(GCTCTA FTGCAC FTTATT ATAAGG ACACAT FCAGCA AATACT FGTTCC BATTCT FCAACA CAAGCT EGGGGA FGGGGA FTGGGG	2781 2841 2901 2961 3021 3081 3141 3201 3321 3381 3441 3501 3561 3621 3625

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 852 amino acids
 (B) TYPE: amino acid

- 83 -

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Phe Ile Phe Met Gly Val Phe Phe Leu Leu Asn Ile Thr Leu Leu Met Ala Asn Phe Ile Asp Pro Arg Cys Phe Trp Arg Ile Asn Leu Asp .25 Glu Ile Thr Asp Glu Tyr Leu Gly Leu Ser Cys Ala Phe Ile Leu Ala Ala Val Gln Thr Pro Ile Glu Lys Asp Tyr Phe Asn Thr Thr Leu Asn Phe Leu Lys Thr Thr Lys Asn His Lys Tyr Ala Leu Ala Leu Val Phe Ala Met Asp Glu Ile Asn Arg Tyr Pro Asp Leu Leu Pro Asn Met Ser Leu Ile Ile Arg Tyr Ser Leu Gly His Cys Asp Gly Lys Thr Val Thr Pro Thr Pro Tyr Leu Phe His Arg Lys Lys Gln Ser Pro Ile Pro Asn Tyr Phe Cys Asn Glu Glu Ser Met Cys Ser Phe Leu Leu Ser Gly Pro Asn Trp Asp Glu Ser Leu Ser Phe Trp Lys Tyr Leu Asp Ser Phe Leu Ser Pro Arg Ile Leu Gln Leu Ser Tyr Gly Ser Phe Ser Ser Ile Phe Ser Asp Asp Glu Gln Tyr Pro Tyr Leu Tyr Gln Met Ala Pro Lys Asp Thr Ser Leu Ala Leu Ala Met Val Ser Phe Ile Leu Tyr Leu Lys Trp Asn Trp Ile Gly Leu Val Ile Pro Asp Asp Gln Gly Asn Gln Phe Leu Leu Glu Leu Lys Lys Gln Ser Glu Asn Lys Glu Ile Cys Phe Ala Phe Val Lys Met Ile Ser Val Asp Glu Val Ser Phe Pro Gln Lys Thr Glu Ile Asn Tyr Lys Gln Ile Val Lys Ser Leu Thr Asn Val Ile Ile Ile Tyr Gly Glu Thr Tyr Asn Phe Ile Asp Leu Ile Phe Arg Met Trp Glu Pro Pro Ile Leu Gln Arg Ile Trp Ile Thr Thr Lys Gln Leu Asn Phe Pro Thr Ser Lys Thr Asp Ile Ser His Asp Thr Phe Tyr Gly Ser Leu Thr Phe Leu Pro His His Gly Glu Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Trp Phe His Leu Arg Asn Thr Asp Leu Cys Leu Val Met Pro Glu Trp Lys Tyr Ile Asn Ser Glu Asp Ser Ala Ser Asn Cys Lys Ile Leu Lys Asn Ser Ser Ser Asp Ala Ser Phe Asp Trp Leu Met Glu Glu Lys Leu Asp Met Ala Phe Ser Glu Asn Ser His Asn Ile Tyr Asn Ala Val His Ala Ile Ala His Ala Leu His Glu Met Asn Leu Gln Gln Ala Asp Asn Gln Ala Ile Asp Asn Gly Lys Gly Ala Ser Ser His Cys Leu Lys Val Asn Ser Phe Leu Arg Arg Thr Tyr Phe Thr Asn Pro Leu Gly Asp Lys Val Phe Met Lys Gln Arg Val Ile Met Gln Asp Glu Tyr.

455 Asp Ile Val His Phe Ala Asn Leu Ser Gln His Leu Gly Ile Lys Met 470 475 Lys Leu Gly Lys Phe Ser Pro Tyr Leu Pro His Gly Arg His Ser His 485 490 Leu Tyr Val Asp Met Ile Glu Leu Ala Thr Gly Arg Arg Lys Met Pro 500 505 Ser Ser Val Cys Ser Ala Asp Cys Ser Pro Gly Phe Arg Arg Leu Trp 515 520 Lys Glu Gly Met Ala Ala Cys Cys Phe Val Cys Ser Pro Cys Pro Glu 535 540 Asn Glu Ile Ser Asn Glu Thr Asn Met Asp Gln Cys Val Asn Cys Pro 550 555 Glu Tyr Gln Tyr Ala Asn Thr Glu Gln Asn Lys Cys Ile Gln Lys Gly 565 570 Val Thr Phe Leu Ser Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Leu 585 590 Met Ala Phe Cys Phe Ser Ala Phe Thr Ala Val Leu Cys Val Phe 600 605 Val Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ser Leu 615 620 Ser Tyr Leu Leu Met Ser Leu Met Phe Cys Phe Leu Cys Ser Phe 630 635 Phe Phe Ile Gly Leu Pro Asn Lys Val Ile Cys Val Leu Gln Gln Ile 645 650 Thr Phe Gly Ile Val Phe Thr Val Ala Val Ser Thr Val Leu Ala Lys 660 665 670 Thr Val Thr Val Val Leu Ala Phe Lys Val Thr Val Pro Gly Arg Arg 675 680 685 Leu Arg Tyr Phe Leu Val Ser Gly Thr Leu Asn Tyr Ile Ile Pro Ile 690 695 700 Cys Ser Leu Leu Gln Cys Val Leu Cys Ala Ile Trp Leu Ala Val Ser 710 715 Pro Pro Phe Val Asp Ile Asp Glu His Ser Gln His Gly His Ile Ile 725 730 Ile Val Cys Asn Lys Gly Ser Val Thr Ala Phe Tyr Cys Val Leu Gly
740 745 740 745 Tyr Leu Ala Cys Leu Ala Leu Gly Ser Phe Thr Leu Ala Phe Leu Ala 755 760 Lys Asn Leu Pro Asp Ala Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser 775 Met Leu Val Phe Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr His 790 795 Ser Thr Lys Gly Lys His Met Val Ala Val Glu Ile Phe Ser Ile Leu 805 810 Ala Ser Ser Ala Gly Met Leu Gly Cys Ile Phe Val Pro Lys Ile Tyr 825 830 Ile Ile Leu Met Arg Pro Glu Arg Asn Ser Thr Gln Lys Ile Arg Glu 840 Lys Ser Tyr Phe 850

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3125 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 1...2169

PCT/US98/13680

- 85 -

(D) OTHER INFORMATION: VR5

(vi)	CECTIENCE	DESCRIPTION:	CEO	TD	MO.Q.
(XI)	SECUENCE	DESCRIPTION:	SEU	111	NU:9:

	()	(1)	SEQUI	ENCE	DESC	CRIP.	LION	SEC	מד נ	NO:	9 :					
			GAA Glu													48
			TCT Ser 20													96
			CTT Leu													144
			CAA Gln													192
TCT Ser 65	CTA Leu	GCA Ala	TTG Leu	GCA Ala	ATG Met 70	GTC Val	TCC Ser	TTC Phe	ATA Ile	CTT Leu 75	TAT Tyr	TTG Leu	AAA Lys	TGG Trp	AAT Asn 80	240
			CTT Leu													288
			AAG Lys 100													336
			ATA Ile													384
			AAA Lys													432
			ACA Thr													480
			TTA Leu													528
		Ser	AAG Lys 180	Thr	Asp	Ile	Ser	His	Asp			Tyr		Ser		576
			CCC Pro													624
			TTC Phe													672
GAG Glu 225	TGG Trp	AAA Lys	TAT Tyr	ATT Ile	AAC Asn 230	TCT Ser	GAA Glu	GAC Asp	TCA Ser	GCA Ala 235	TCT Ser	AAT Asn	TGT Cys	AAA Lys	ATA Ile 240	720

									•							-
				TCA Ser 245												768
				GCC Ala												816
				GCC Ala												864
				ATA Ile												912
				TTT Phe												960
				ATG Met 325												1008
				GCG Ala												1056
				AGC Ser												1104
				ATT Ile												1152
				GCA Ala												1200
				GCC Ala 405												1248
		Ser	Asn	GAG Glu	Thr	Asn	Met	Asp	Gln	Сув	Val	Asn		Pro		1296
				AAC Asn											GTC Val	1344
				TAT											ATG Met	1392
				TCT Ser												1440
				ACT Thr 485												1488
TAT	CTA	TTA	CTC	ATG	TCA	CTC	ATG	TTC	TGT	TTT	CTG	TGC	TCC	TTT	TTC .	1536

										-							_
	Tyr	Leu	Leu	Leu 500	Met	Ser	Leu	Met	Phe 505	Сув	Phe	Leu	Cys	Ser 510	Phe	Phe	
						AAC Asn											1584
	TTT Phe	GGA Gly 530	ATT Ile	GTA Val	TTT Phe	ACT Thr	GTA Val 535	GCT Ala	GTT Val	TCC Ser	ACA Thr	GTT Val 540	CTG Leu	GCC Ala	AAA Lys	ACA Thr	1632
	GTC Val 545	ACT Thr	GTG Val	GTT Val	CTA Leu	GCT Ala 550	TTC Phe	AAA Lys	GTC Val	ACA Thr	GAC Asp 555	CCA Pro	GGA Gly	AGA Arg	AGA Arg	TTG Leu 560	1680
	AGA Arg	TAC Tyr	TTC Phe	CTT Leu	GTA Val 565	TCA Ser	GGG Gly	ACA Thr	CTA Leu	AAC Asn 570	TAC Tyr	ATT Ile	ATT Ile	CCT Pro	ATA Ile 575	TGT Cys	1728
	TCC Ser	CTA Leu	CTC Leu	CAA Gln 580	TGT Cys	GTT Val	CTG Leu	TGT Cys	GCA Ala 585	ATC Ile	TGG Trp	CTA Leu	GCA Ala	GTC Val 590	TCT Ser	CCT Pro	1776
	CCC Pro	TTT Phe	GTT Val 595	GAT Asp	ATT Ile	GAT Asp	GAA Glu	CAC His 600	TCT Ser	CAG Gln	CAT His	GGC Gly	CAC His 605	ATC Ile	ATC Ile	ATT Ile	1824
	GTG Val	TGC Cys 610	AAC Asn	AAG Lys	GGC Gly	TCA Ser	GTT Val 615	ACT Thr	GCA Ala	TTC Phe	TAC Tyr	TGT Cys 620	GTC Val	CTT Leu	GGA Gly	TAC Tyr	1872
	TTG Leu 625	GCC Ala	TGC Cys	CTG Leu	GCA Ala	CTG Leu 630	GGA Gly	AGC Ser	TTC Phe	ACT Thr	TTG Leu 635	GCT Ala	TTC Phe	TTG Leu	GCC Ala	AAG Lys 640	1920
						TTC Phe											1968
						GTC Val											2016
•	ACA Thr	AAG Lys	GGC Gly 675	AAA Lys	CAC His	ATG Met	GTT Val	GCT Ala 680	GTG Val	GAG Glu	ATC Ile	TTC Phe	TCC Ser 685	ATC Ile	TTG Leu	GCA Ala	2064
i	TCC Ser	AGT Ser 690	GCA Ala	GGG Gly	ATG Met	CTT Leu	GAA Glu 695	TGT Cys	ATT Ile	TTT Phe	GTA Val	CCC Pro 700	AAG Lys	ATT Ile	TAT Tyr	ATC Ile	2112
	ATT Ile 705	TTA Leu	ATG Met	AGA Arg	CCA Pro	GAG Glu 710	AGA Arg	AAT Asn	TCT Ser	ACC Thr	CAA Gln 715	AAG Lys	ATC Ile	AGG Arg	GAA Glu	AAA Lys 720	2160
		TAT Tyr		TGAZ	CAAZ	ATA 1	TTAC	GAAT	rr ci	rgtc <i>i</i>)TAA!	TA	\agti	rggt	ACAT	TAACCA	2218
•	GTGA TCAT CTTC GTTT	TAAA TCAC GTTT TAATC	AAG (CTT 1 CTG 1 CCA (SAAGT CTTC ATTTC CCACT	PATCA CATT CATGO PTTGO	AT AT TT CT SA GA TG TA	CTAC CTCA CTTGC VAADA	TGAZ AGAGZ CCT(AAAA	A CTTA A ACT C TGO C GAO	PATGT PAAAC STAAC SATCT	TACA ETCT ETTC TAGG	GTGT CTAI CAAI ACAG	CCAT ATTAT AAAC AAAE	TAA A TTA C CGT T EGG T	AATCT CAATT FGATI FTACI	GCTCTA FTGCAC FTTATT AAGGCA ACATAG AGCAAA	2278 2338 2398 2458 2518 2578

- 88 -

GTTGAAATCA	GAATTATTTT	CTGATTTCCA	GTAAGAGCAC	ACACAGAAGA	AAATACTGAC	2638
TTTTTTTTC	TTCTGTTCTT	CAAGCTACTG	GCCAATAATC	TAAGGAGGAA	ATGTTCCTTT	2698
TCTGCTGTCA	AATACAAATA	TATTATATCC	AACAATGATC	AGAAGCCCAG	GGATTCTGTG	2758
GCTGAATTGG	GAATATTTGG	AAGAAGCTGA	GGAGGAGGGT	GACCAGCATT	CTCAACAAAC	2818
CTGGACAAGC	AAGATCTCTC	AGACACTGAG	CCTCTAACCA	GAGATCATAC	ACAAGCTGAT	2878
GTGAAGCCCC	CAACAAATAT	GCACCATAAG	ACTGCCTGGT	CTAGCATCAG	TGGGAGACAC	2938
ACCTAACCCC	AGAGAGACTT	AAGTCCCCAG	GGATTGGGAA	GTGCTGGGCA	TTGAGGATGT	2998
AGGGATATCA	TCTTTGAGAT	GGCAGAGGAG	TTGTTAGATG	AGGAAGAGTC	AGGGGGCAA	3058
ACCAGGAAGG	GGATAACTAC	TAGATTGTAA	CAAAAATATT	GAGTAATAAT	AAATTAAAA	3118
ATGAAAT						3125

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 723 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Ile Cys Asn Glu Glu Ser Met Cys Ser Phe Leu Leu Ser Gly Pro Asn 10 Trp Asp Glu Ser Leu Ser Phe Trp Lys Tyr Leu Asp Ser Phe Leu Ser . 20 Pro His Ile Leu Gln Leu Ser Tyr Gly Ser Phe Ser Ser Ile Phe Ser 40 45 Asp Asp Glu Gln Tyr Pro Tyr Leu Tyr Gln Met Ala Pro Lys Asp Thr 55 Ser Leu Ala Leu Ala Met Val Ser Phe Ile Leu Tyr Leu Lys Trp Asn 70 75 Trp Ile Gly Leu Val Ile Pro Asp Asp Asp Gln Gly Asn Gln Phe Leu 85 90 Leu Glu Leu Lys Lys Gln Ser Glu Asn Lys Glu Ile Cys Phe Ala Phe 100 105 110 Val Lys Met Ile Ser Val Asp Glu Val Ser Phe Pro Gln Lys Thr Glu 115 120 125 Ile Tyr Tyr Lys Gln Ile Val Lys Ser Leu Thr Asn Val Ile Ile Ile 130 135 140 Tyr Gly Glu Thr Tyr Asn Phe Ile Asp Leu Ile Phe Arg Met Trp Glu 150 155 Pro Pro Ile Leu Gln Arg Ile Trp Ile Thr Thr Lys Gln Leu Asn Phe 165 170 Pro Thr Ser Lys Thr Asp Ile Ser His Asp Thr Phe Tyr Gly Ser Leu 180 185 190 Thr Phe Leu Pro His His Gly Glu Ile Ser Gly Phe Lys Asn Phe Val 200 205 Gln Thr Trp Phe His Leu Arg Asn Thr Asp Leu Tyr Leu Val Met Pro 215 220 Glu Trp Lys Tyr Ile Asn Ser Glu Asp Ser Ala Ser Asn Cys Lys Ile 230 235 Leu Lys Asn Ser Ser Ser Asp Ala Ser Phe Asp Trp Leu Met Glu Gln 245 250 255 Lys Leu Asp Met Ala Phe Ser Asp Asn Ser His Asn Ile Tyr Asn Val 260 265 270 Val His Ala Ile Ala His Ala Leu His Glu Met Asn Leu Gln Gln Ala 275 280 285 Asp Asn Gln Ala Ile Asp Asn Gly Lys Gly Ala Ser Ser His Cys Leu 290 295 300 Lys Val Asn Ser Phe Leu Arg Arg Thr Tyr Phe Thr Asn Pro Leu Gly 310 315 Asp Lys Val Phe Met Lys Gln Arg Val Ile Met Gln Asp Glu Tyr Asp.

330 325 Ile Val His Phe Ala Asn Leu Ser Gln His Leu Gly Ile Lys Met Lys 340 345 350 Leu Gly Lys Phe Ser Pro Tyr Leu Pro His Gly Arg His Ser His Leu 355 360 365 Tyr Val Asp Met Ile Glu Leu Ala Thr Gly Arg Arg Lys Met Pro Ser 375 370 380 Ser Val Cys Ser Ala Asp Cys Ser Pro Gly Phe Arg Arg Leu Trp Lys 390 395 Glu Gly Met Ala Ala Cys Cys Phe Val Cys Ser Pro Cys Pro Glu Asn 405 410 Glu Ile Ser Asn Glu Thr Asn Met Asp Gln Cys Val Asn Cys Pro Glu 425 Tyr Gln Tyr Ala Asn Thr Glu Gln Asn Lys Cys Ile Gln Lys Gly Val 440 445 Thr Phe Leu Ser Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Leu Met 455 460 Ala Phe Cys Phe Ser Ala Phe Thr Ala Val Val Leu Cys Val Phe Val 470 475 Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ser Leu Ser 485 490 Tyr Leu Leu Met Ser Leu Met Phe Cys Phe Leu Cys Ser Phe Phe 505 Phe Ile Gly Leu Pro Asn Lys Val Ile Cys Val Leu Gln Gln Ile Thr 515 520 525 Phe Gly Ile Val Phe Thr Val Ala Val Ser Thr Val Leu Ala Lys Thr 540 530 535 Val Thr Val Val Leu Ala Phe Lys Val Thr Asp Pro Gly Arg Arg Leu 550 555 Arg Tyr Phe Leu Val Ser Gly Thr Leu Asn Tyr Ile Ile Pro Ile Cys 570 565 Ser Leu Leu Gln Cys Val Leu Cys Ala Ile Trp Leu Ala Val Ser Pro 580 585 590 Pro Phe Val Asp Ile Asp Glu His Ser Gln His Gly His Ile Ile Ile 595 600 605 Val Cys Asn Lys Gly Ser Val Thr Ala Phe Tyr Cys Val Leu Gly Tyr 610 620 Leu Ala Cys Leu Ala Leu Gly Ser Phe Thr Leu Ala Phe Leu Ala Lys 630 635 Asn Leu Pro Asp Ala Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met 645 650 Leu Val Phe Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr His Ser 660 665 670 Thr Lys Gly Lys His Met Val Ala Val Glu Ile Phe Ser Ile Leu Ala 675 680 Ser Ser Ala Gly Met Leu Glu Cys Ile Phe Val Pro Lys Ile Tyr Ile 695 700 Ile Leu Met Arg Pro Glu Arg Asn Ser Thr Gln Lys Ile Arg Glu Lys 705 710 Ser Tyr Phe

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1889 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GAATTCGGCT TCTGCACCAA ATGGCGACGA AAGACACATC TCTTTCACTT GCCATTGTTT 60 CTTTGATGGT TCATTTTAGG TGGTCTTGGG TTGGTCTAAT TCTCCCAGAT GACCACAAAG 120 GAAATAAAAT ACTATCAGAT TTTAGAAAGG AGATGGAAAG AAAAAGAATC TGTACGGCTT TTGTAAAAAT GATTCCTGCC ACATGGACTT CATCTTTTGT CAAATTCTGG GAAAATATGG 240 ATGACACCAA CATAATAATT ATTTATGGTG ACATTGATTC TCTAGAAGGT CTAATGCGAA 300 ATATTGGGCA AAGGTTATTG ACATGGCATG TCTGGGTCAT GAACATTGAA CCCCATATTA TTGAATATGA TAATTATTTC ATGTTAGATT CATTCCATGG AAGTTTAATT TTTAAGCACA 420 ATTATAGAGA GAATTTTGAG TTTACCAAAT TTATTCGAAC AGTTAATCCT AAAAAATACC CAGAAGACAT TTATCTCCCT AAGATGTGGT ATTTGTTCTT CATGTGCTCA TTTTCTGATA 540 TTAATTGTCA AGTTTTGGAC AGCTGTCAAA CAAATGCTTC TTTGGATATG TTACCTAGTC AGATATTTGA TGTGGTCATG AGTGAAGAGA GCACAAGTAT TTACAATGCT GTGTACGCTG 660 TGGCTCACAG CCTCCATGAG ATGAGACTTC AGCAACTTCA AACACAACCG TGTGAAAATG AAGAAGGGAT GGAGTTCTTT CCATGGCAGC TTAATACTTT CCTGAAGGAT ATTGAGGTGA 780 GAGTCAACAG TTTAGACTGG AGACAGAGAA TAGATGCTGA ATATGACATT CTTAACCTCT GGAATTTACC AAAGGGTCTT GGACTAAAAG TGAAAATAGG AAACTTTTAT GCAAATGCTC 900 CCCAGGGTCA ACAATTGTCT TTATCTGAAC AGATGATTCA ATGGCCAGAA ATATTTTCAG AGATCCCTCA GTCGGTGTGC AGTGAGAGTT GTGGGCCTGG ATTCAGGAAA GTAACCCTGG 1020 AGAATAAGGC TATCTGCTGC TACAATTGTA CTCCCTGTGC AGACAATGAG ATTTCTAATG AGACAGATGT AGACCAGTGT GTGAAGTGTC CAGAGAGTCA TTATGCAAAT ACAGAGAAGA GCAACTGCTA TCAAAAGTCT GTGAGCTTTC TGGGCTATGA AGACCCTTTG GGGATGGCTC 1200 TAGCCAGCAT AGCTTTGTGC TTGTCTGCAC TAACTGCCTT TGTTATTGGC ATATTTGTGA AACACAAAGA CACTCCTATT GTTAAGGCCA ATAATCAAGC TCTGAGTTAC ACTTTGCTCA 1320 TCACACTCAA ATTCTGTTTC CTATGTTCTT TGAACTTCAT TGGTCAGCCC AACACAGTTG CCTGCATCCT TCAGCAGACC ACCTTTGCAG TTGCTTTCAC TATGGCTCTT GCCACTGTGT TGGCCAAAGC TATCACTGTG GTTCTTGCCT TTAAGGTCAG TTTTCCAGGG AGAATGGTAA GATGGCTAAT GATATCAAGG GGTCCAAACT ATATCATTCC TATCTGCACC CTGATCCAAC 1560 TTCTTCTTTG TGGAATATGG ATGGCAATAT CTCCACCATA CATTGACCAA GATGCTCATA TTGAACATGG TCACATCATC ATTTTGTGCA ACAAGGGCTC AGCTGTTGCC TTCCACTCTG 1680 TCCTGGGATA CCTCTGCTTC TTGGCCCTTG GGAGTTATAC CATGGCCTTC TTGTCAAGAA ATTTGCCTGA TACATTCAAC GAATCCAAAT TTATCTCACT AAGTATGCTG GTATTCTTCT 1800 GTGTCTGGAT CACCTTTCTT CCTGTCTACC ACAGCACTAA AGGGAAGGTC ATGGTCGCCG 1860 TCGAGGTCTT TTGCATCCAA GCCGAATTC 1889

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 604 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ser Leu Ser Leu Ala Ile Val Ser Leu Met Val His Phe Arg Trp Ser 10 Trp Val Gly Leu Ile Leu Pro Asp Asp His Lys Gly Asn Lys Ile Leu 25 20 Ser Asp Phe Arg Lys Glu Met Glu Arg Lys Arg Ile Cys Thr Ala Phe 40 Val Lys Met Ile Pro Ala Thr Trp Thr Ser Ser Phe Val Lys Phe Trp 55 60 Glu Asn Met Asp Asp Thr Asn Ile Ile Ile Tyr Gly Asp Ile Asp Ser Leu Glu Gly Leu Met Arg Asn Ile Gly Gln Arg Leu Leu Thr Trp 85 90 His Val Trp Val Met Asn Ile Glu Pro His Ile Ile Glu Tyr Asp Asn 105 100 110 Tyr Phe Met Leu Asp Ser Phe His Gly Ser Leu Ile Phe Lys His Asn 120 Tyr Arg Glu Asn Phe Glu Phe Thr Lys Phe Ile Arg Thr Val Asn Pro 130 135 140 Lys Lys Tyr Pro Glu Asp Ile Tyr Leu Pro Lys Met Trp Tyr Leu Phe 150 155

Phe Met Cys Ser Phe Ser Asp Ile Asn Cys Gln Val Leu Asp Ser Cys Gln Thr Asn Ala Ser Leu Asp Met Leu Pro Ser Gln Ile Phe Asp Val Val Met Ser Glu Glu Ser Thr Ser Ile Tyr Asn Ala Val Tyr Ala Val Ala His Ser Leu His Glu Met Arg Leu Gln Gln Leu Gln Thr Gln Pro Cys Glu Asn Glu Glu Gly Met Glu Phe Phe Pro Trp Gln Leu Asn Thr Phe Leu Lys Asp Ile Glu Val Arg Val Asn Ser Leu Asp Trp Arg Gln Arg Ile Asp Ala Glu Tyr Asp Ile Leu Asn Leu Trp Asn Leu Pro Lys Gly Leu Gly Leu Lys Val Lys Ile Gly Asn Phe Tyr Ala Asn Ala Pro Gln Gly Gln Gln Leu Ser Leu Ser Glu Gln Met Ile Gln Trp Pro Glu Ile Phe Ser Glu Ile Pro Gln Ser Val Cys Ser Glu Ser Cys Gly Pro Gly Phe Arg Lys Val Thr Leu Glu Asn Lys Ala Ile Cys Cys Tyr Asn Cys Thr Pro Cys Ala Asp Asn Glu Ile Ser Asn Glu Thr Asp Val Asp Gln Cys Val Lys Cys Pro Glu Ser His Tyr Ala Asn Thr Glu Lys Ser Asn Cys Tyr Gln Lys Ser Val Ser Phe Leu Gly Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Ser Ile Ala Leu Cys Leu Ser Ala Leu Thr Ala Phe Val Ile Gly Ile Phe Val Lys His Lys Asp Thr Pro Ile Val Lys Ala Asn Asn Gln Ala Leu Ser Tyr Thr Leu Leu Ile Thr Leu Lys Phe Cys Phe Leu Cys Ser Leu Asn Phe Ile Gly Gln Pro Asn Thr Val Ala Cys Ile Leu Gln Gln Thr Thr Phe Ala Val Ala Phe Thr Met Ala Leu Ala Thr Val Leu Ala Lys Ala Ile Thr Val Val Leu Ala Phe Lys Val Ser Phe Pro Gly Arg Met Val Arg Trp Leu Met Ile Ser Arg Gly Pro Asn Tyr Ile Ile Pro Ile Cys Thr Leu Ile Gln Leu Leu Cys Gly Ile Trp Met Ala Ile Ser Pro Pro Tyr Ile Asp Gln Asp Ala His Ile Glu His Gly His Ile Ile Leu Cys Asn Lys Gly Ser Ala Val Ala Phe His Ser Val Leu Gly Tyr Leu Cys Phe Leu Ala Leu Gly Ser Tyr Thr Met Ala Phe Leu Ser Arg Asn Leu Pro Asp Thr Phe Asn Glu Ser Lys Phe Ile Sér Leu Ser Met Leu Val Phe Phe Cys Val Trp Ile Thr Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys Val

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1889 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

WO 99/00422 PCT/US98/13680 - 92 -

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCGGCT	TCTGCATCAA	ATGGCGACGA	AGGACACATC	TCTTTCACTT	GCCATTGTTT	60
CTTTGATGGT	TCATTTTAGG	TGGTCTTGGG	TTGGTCTAAT	TCTCCCAGAT	GACCACAAAG	120
GAAATAAAAT	ACTATCAGAT	TTTAGAAAGG	AGATGGAGAG	AAAAAGAATC	TGTACGGCTT	180
TTGTAAAAAT	GATTCCTGCC	ACATGGACTT	CATCTTTTGT	CAAATTCTGG	GAAAATATGG	240
ATGACACCAA	CATAATAATT	ATTTATGGTG	ACATTGATTC	TCTAGAAGGT	CCAATGCGAA	300
ATATTGGGCA	AAGGTTATTG	ACATGGCATG	TCTGGGTCAT	GAACATTGAA	CCCCATATTA	360
TTGAATATGA	TAATTATTTC	ATGTTAGATT	CATTCCATGG	AAGTTTAATT	TTTAAGCACA	420
ATTATAGAGA	GAATTTTGAG	TTTACCAAAT	TTATTCGAAC	AGTTAATCCT	AAAAAATACC	480
CAGAAGACAT	TTATCTCCCT	AAGATGTGGT	ATTTGTTCTT	CATGTGCTCA	TTTTCTGATA	540
TTAATTGTCA	AGTTTTGGAC	AGCTGTCAAA	CAAATGCTTC	TTTGGATATG	TTACCTAGTC	600
AGATATTTGA	TGTGGTCATG	AGTGAAGAGA	GCACAAGTAT	TTACAATGCT	GTGTACGCTG	660
TGGCTCACAG	CCTCCATGAG	ATGAGACTTC	AGCAACTTCA	AACACAACCG	TGTGAAAATG	720
AAGAAGGGAT	GGAGTTCTTT	CCATGGCAGC	TTAATACTTT	CCTGAAGGAT	ATTGAGGTGA	780
GAGTCAACAG	TTTGGACTGG	AGACAGAGAA	TAGATGCTGA	ATATGACATT	CTTAACCTCT	840
GGAATTTACC	AAAGGGTCTT	GGACTAAAAG	TGAAAATAGG	AAACTTTTAT	GCAAATGCTC	900
CCCAGGGTCA	ACAATTGTCT	TTATCTGAAC	AGATGATTCA	ATGGCCAGAA	ATATTTTCAG	960
AAGTCCCTCA	GTCTGTGTGC	AGTGAGAGTT	GTAGGCCTGG	ATTCAGGAAA	GTATCCCTGG	1020
ATGATAAGGC	CATCTGCTGC	TACAAGTGCA	CTCCTTGTGC	CGACAATGAG	ATATCTAATG	1080
AGACAGATGT	AGACCAGTGT	GTGAAGTGTC	CAGAGAGTCA	TTATGCAAAT	ACAGAGAAGA	1140
GCAACTGCTT	CCCAAAATCT	GTGAGCTTTC	TGGCCTATGA	AGACCCCTTG	GGGATGGCTC	1200
TAGCCAGCAT	AGCTTTGTGC	TTATCTGCAC	TCACTGTCTT	TGTTATTGGC	ATCTTTGTGA	1260
AAAACAGAGA	CACTCCTATT	GTCAAGGCCA	ATAATCGGAC	TCTAAGTTAC	ATTTTGCTCA	1320
TCACACTCAC	CTTTTGTTTC		TGAACTTCAT	TGGTCAGCCC	AACACAGCTG	1380
CCTGCATCCT	TCAGCAGACC		TTGCTTTCAC	TATGGCTCTT	GCCACTGTGT	1440
TGGCCAAAGC	TATTACTGTA	GTCCTTGCCT	TTAAGATCAG	TTTTCCAGGG	AGAATGTTAA	1500
GGTGGCTAAT	GATATCAAGG	GGTCCAAGAT	ACATCATTCC	TATCTGCACA	CTGATCCAGC	1560
TTCTTCTTTG	TGGAATATGG	ATGGCAACTT	CTCCACCATT	CATTGACCAA	GATGTTAATA	1620
CTGAAGATGG	ATACATCATC	CTTTTGTGCA	ACAAGGGCTC	AGCTGTTGCC	TTCCATTCAG	1680
TCCTGGGATA	CCTCTGTTTC	TTGGCCCTTG	GGAGTTATAC	CATGGCCTTC	TTGTCTAGAA	1740
ATTTGCCTGA	TACATTCAAT	GAATCCAAAT	TTCTGTCATT	CAGTATGCTG	GTGTTCTTCT	1800
GTGTCTGGGT	CACCTTTCTT	CCTGTCTACC	ACAGCACTAA	AGGGAAAGTT	ATGGTCGTCG	1860
TCGAAGTCTT	CTGCATCCAA	GCCGAATTC				1889

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 604 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ser Leu Ser Leu Ala Ile Val Ser Leu Met Val His Phe Arg Trp Ser 10 15 Trp Val Gly Leu Ile Leu Pro Asp Asp His Lys Gly Asn Lys Ile Leu 20 25 Ser Asp Phe Arg Lys Glu Met Glu Arg Lys Arg Ile Cys Thr Ala Phe 35 40 Val Lys Met Ile Pro Ala Thr Trp Thr Ser Ser Phe Val Lys Phe Trp 55 Glu Asn Met Asp Asp Thr Asn Ile Ile Ile Ile Tyr Gly Asp Ile Asp 70 Ser Leu Glu Gly Pro Met Arg Asn Ile Gly Gln Arg Leu Leu Thr Trp 85 90 His Val Trp Val Met Asn Ile Glu Pro His Ile Ile Glu Tyr Asp Asn 100 105

Tyr Phe Met Leu Asp Ser Phe His Gly Ser Leu Ile Phe Lys His Asn Tyr Arg Glu Asn Phe Glu Phe Thr Lys Phe Ile Arg Thr Val Asn Pro Lys Lys Tyr Pro Glu Asp Ile Tyr Leu Pro Lys Met Trp Tyr Leu Phe Phe Met Cys Ser Phe Ser Asp Ile Asn Cys Gln Val Leu Asp Ser Cys Gln Thr Asn Ala Ser Leu Asp Met Leu Pro Ser Gln Ile Phe Asp Val Val Met Ser Glu Glu Ser Thr Ser Ile Tyr Asn Ala Val Tyr Ala Val Ala His Ser Leu His Glu Met Arg Leu Gln Gln Leu Gln Thr Gln Pro Cys Glu Asn Glu Glu Gly Met Glu Phe Phe Pro Trp Gln Leu Asn Thr Phe Leu Lys Asp Ile Glu Val Arg Val Asn Ser Leu Asp Trp Arg Gln Arg Ile Asp Ala Glu Tyr Asp Ile Leu Asn Leu Trp Asn Leu Pro Lys Gly Leu Gly Leu Lys Val Lys Ile Gly Asn Phe Tyr Ala Asn Ala Pro Gln Gly Gln Gln Leu Ser Leu Ser Glu Gln Met Ile Gln Trp Pro Glu Ile Phe Ser Glu Val Pro Gln Ser Val Cys Ser Glu Ser Cys Arg Pro Gly Phe Arg Lys Val Ser Leu Asp Asp Lys Ala Ile Cys Cys Tyr Lys Cys Thr Pro Cys Ala Asp Asn Glu Ile Ser Asn Glu Thr Asp Val Asp Gln Cys Val Lys Cys Pro Glu Ser His Tyr Ala Asn Thr Glu Lys Ser Asn Cys Phe Pro Lys Ser Val Ser Phe Leu Ala Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Ser Ile Ala Leu Cys Leu Ser Ala Leu Thr Val Phe Val Ile Gly Ile Phe Val Lys Asn Arg Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Thr Leu Ser Tyr Ile Leu Leu Ile Thr Leu Thr Phe Cys Phe Leu Cys Ser Leu Asn Phe Ile Gly Gln Pro Asn Thr Ala Ala Cys Ile Leu Gln Gln Thr Thr Phe Ala Val Ala Phe Thr Met Ala Leu Ala Thr Val Leu Ala Lys Ala Ile Thr Val Val Leu Ala Phe Lys Ile Ser Phe Pro Gly Arg Met Leu Arg Trp Leu Met Ile Ser Arg Gly Pro Arg Tyr Ile Ile Pro Ile Cys Thr Leu Ile Gln Leu Leu Cys Gly Ile Trp Met Ala Thr Ser Pro Pro Phe Ile Asp Gln Asp Val Asn Thr Glu Asp Gly Tyr Ile Ile Leu Leu Cys Asn Lys Gly Ser Ala Val Ala Phe His Ser Val Leu Gly Tyr Leu Cys Phe Leu Ala Leu Gly Ser Tyr Thr Met Ala Phe Leu Ser Arg Asn Leu Pro Asp Thr Phe Asn Glu Ser Lys Phe Leu Ser Phe Ser Met Leu Val Phe Phe Cys Val Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys Val

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:

 (A) LENGTH: 2561 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

 (ii) MOLECULE TYPE: cDNA
 (ix) FEATURE:

 (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 80...349
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

(D) OTHER INFORMATION: VR8

ATAGGTGCAA CTGTGTGTGT GATGTTTTC TACATCAGAA ACGGATTTCA CAACAGCTCC ATCTTAGATC CTAGCAGAC ATG AAG AAG CTC TGT GCT TTC ACG ATT TCA TTG Met Lys Lys Leu Cys Ala Phe Thr Ile Ser Leu 1 5 10	60 112
TTG TTT CTG AAG TTT TCT CTC ATC TTG TGC TGT TGG AGT GAA CCA AGT Leu Phe Leu Lys Phe Ser Leu Ile Leu Cys Cys Trp Ser Glu Pro Ser 15 20 25	160
TGC TTT TGG AGG ATA AAG AAT AGT GAT GAT AAT GAC GGA GAT TTG CAA Cys Phe Trp Arg Ile Lys Asn Ser Asp Asp Asn Asp Gly Asp Leu Gln 30 35 40	208
AGG GAA TGT CAT TTT TAC CTT GGG GCA GCT GAT ACA CCA GTT GAA GAT Arg Glu Cys His Phe Tyr Leu Gly Ala Ala Asp Thr Pro Val Glu Asp 45 50 55	256
AAT TTT TAT AGT TCA CTT TTA AAA TTT AGG TTT TCT TTG GAC CAT TTA Asn Phe Tyr Ser Ser Leu Leu Lys Phe Arg Phe Ser Leu Asp His Leu 60 70 75	304
ATC CTA ACC TAC GCG ACC ATG ACC GGC TGC CCC ATG TCC ATC AGG TAGCC Ile Leu Thr Tyr Ala Thr Met Thr Gly Cys Pro Met Ser Ile Arg 80 85 90	354
CCCAAGGACA CACATTTGTC CCATGGCATG GTCTCCTTGA TGTTTCACTT TAGATGGACT	414
TGGATAGGAA TGGTCATCTC AGATGATGAC CAGGGTATTC AGTTTCTCTC AGATTTAAGA	474
GAAGAAAGCC AAAGGCATGG GATCTGTTTA GCTTTTGTTA ATATGATCCC AGAAAACATG CAGATATACA TGACAAGGGC TACAATATAT GATCAACAAA TTATGACATC TTCAGCAAAG	534 594
GTTGTTATCA TTTATGGTGA AATGAACTCT ACTCTAGAAG TAAGCTTTAG AAGATGGGAA	654
GAGTTAGGTG CTCGGAGAAT CTGGATCACA ACCTCACAAT GGGATGTCAT CACAAATAAA	714
AAAGACTTCA CCCTTAATCT CTTCCATGGG ACTATCACTT TTGCACACCA CAGAGTTGAG	774
ATTCCTAAAT TAAATAAATT CATGCAAACA ATGAACACTG CCAAATACCC AGTAGATATT	834
TCTCATACTA TATTGGAGTG GAATTATTTT AATTGTTCAA TATCTAAGAA CAGCATTAGA	894
ATGCATCATA TTACATTCAA CAACACCTTG GAATGGACAT CACTGCACAA CTATGATATG	954
GCGATGAGTG ATGAAGGTTA CAGTTTATAT AATGCTGTTT ATGCTGTGGC CCACACCTAC CATGAATACA TTTTTCAACA AGTAGAGTCT CAGAAAAAGG CAAAACCCAA AAGATATTTC	1014 1074
ACTGCTTGTC AGCAGCCTCA GGTTCCCTCC TCCGTGTGTA GTGTGGCATG TACTGCTGGA	1134
TTCAGGAAAA TTTATCAAAA AGAAACAGCA GACTGCTGCT TTGATTGTGT TCAGTGCCCA	1194
GAAAATGAGA TTTCCAACGA AACAGATATG GAACAGTGTG TGAGGTGTCC AGATGATAAG	1254
TATGCCAACA TAGAGCAAAC CCACTGCCTC TCAAGAGCTG TATCATTTCT GGCTTATGAA	1314
GATCCATTGG GGATGGCTCT AGGCTGCATG GCACTGTCCT TCTCGGCCAT CACAATTCTA	1374
GTCCTCGTCA CATTTGTGAA ACACAACGAT ACTCCCATTG TGAAGGCCAA TAACCGCATT	1434
CTCAGCTACA TCCTGCTCAT CTCTCTCGTC TTCTGCTTCC TCTGCTCCCT GCTCTTCATT GGACCTCCCG ACCAGGTCAC CTGCATCTTG CAGCAGACCA CATTTGGAGT ATTTTTCACT	1494 1554
GTGTCTGTTT CTACAGTGTT GGCCAAAACA ATAACTGTGG TCATGGCTTT CAAGCTCACT	1614
ACTCCAGGAA GAAGGATGAG AGGGATGATG ATGACAGGGG CACCTAAGTT GGTCATTCCC	1674
ATTTGTACCC TGATCCAACT TGTTCTCTGT GGAATCTGGT TGGTCACATC TCCTCCCTTT	1734
ATTGACAGAG ATATACAATC TGAGCATGGG AAGATTGTCA TTCTTTGCAA TAAAGGCTCA	1794

GTCATTGCCT	TCCACGTCGT	CCTGGGATAC	TTGGGCTCCT	TGGCTCTGGG	GAGCTTCACT	1854
TTGGCTTTCT	TGGCTAGGAA	CCTTCCTGAC	ACATTCAATG	AAGCCAAGTT	CCTAACTTTC	1914
AGCATGCTGG	TGTTCTGCAG	TGTCTGGATC	ACCTTCCTCC	CTGTCTACCA	CAGCACCAGG	1974
GGGAGGGTCA	TGGTGGTTGT	GGAGGTTTTC	TCCATCTTGG	CTTCTAGTGC	AGGGTTGCTA	2034
ATGTGTATCT	TTGTCCCAAA	GTGTTATGTT	ATTTTAATTA	GACCAGATTC	AAATATTATA	2094
AAGAAACATA	AAGGTAAAGT	GCTTAATTGA	AACTTTCATG	GTATGAAAAT	GTTAGATGAT	2154
ATTCAACTTA	TCTTATTCTT	CATCTTAATA	AAAGCAGTAC	TTCATCATAT	AAAAAATAAA	2214
GTAATATACA	GATTTATACT	TACAAACTGG	ACAGCAAACA	TGAATATGTT	GAGAACTGGG	2274
ATTCTCAATT	GAGGAATGGC	TACCAACATT	TTGATCTGTG	GTTTTGTGTT	TAAGCCATGC	2334
ACTTAATTAA	TGATTAACAT	GAGGTTACCC	TACTGTCTGT	GAACAGCGCC	ACCTCTAGGC	2394
ATGCTGTCCT	TGAGTTATAA	GAAAGGGTAC	TGCATACACA	ATGGACATGA	AGCCAGTAAT	2454
CAACATTATT	CCACTTGCTT	TCATGGAGTT	CTTACTTCCA	AGTTCATGCC	TTGACTTTAT	2514
TCAATGTTCT	ATGACAAAGG	TAGATAAATA	AATAAACACT	TTTCCTC		2561

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 90 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

 Met
 Lys
 Lys
 Leu
 Cys
 Ala
 Phe
 Thr
 Ile
 Ser
 Leu
 Leu
 Lys
 Phe

 Ser
 Leu
 Ile
 Leu
 Cys
 Cys
 Trp
 Ser
 Glu
 Pro
 Ser
 Cys
 Phe
 Trp
 Arg
 Ile
 30
 Ile
 30
 Ile
 Arg
 Ile
 Ile

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2734 base pairs
 - (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 80...1387
 - (D) OTHER INFORMATION: VR9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

ATAGGTGCAA CTGTGTGTGT GATGTTTTTC TACATCAGAA ACGGATTTCA CAACAGCTCC

ATCTTAGATC CTAGCAGAC ATG AAG AAG CTC TGT GCT TTC ACG ATT TCA TTG

Met Lys Lys Leu Cys Ala Phe Thr Ile Ser Leu

1 5 10

TTG TTT CTG AAG TTT TCT CTC ATC TTG TGC TGT TGG AGT GAA CCA AGT
Leu Phe Leu Lys Phe Ser Leu Ile Leu Cys Cys Trp Ser Glu Pro Ser

- 96 -

						-				
		15			20			25		
									TTG Leu	208
									GAA Glu	256
	 								GAA Glu	304
_									AGG Arg 90	352
				Thr					GGT Gly	400
									CAA Gln	448
						_			GAT Asp	496
									AAA Lys	544
									AAT Asn 170	592
									GCC Ala	640
									CAC His	688
									GGT Gly	736
		_					•		ATC Ile	784
									ATG Met 250	832
						Met			AAG Lys	880
		Tyr			Ser			Ser	TTT Phe	928

AGA TGG GAA GAG TTA GGT GCT CGG AGA ATC TGG ATC ACA ACC TCA CAA Arg Trp Glu Glu Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln 285 290 295	976
TGG GAT GTC ATC ACA AAT AAA AAA GAC TTC ACC CTT AAT CTC TTC CAT Trp Asp Val Ile Thr Asn Lys Lys Asp Phe Thr Leu Asn Leu Phe His 300 305 310	1024
GGG ACT ATC ACT TTT GCA CAC CAC AGA GTT GAG ATT CCT AAA TTA AAT Gly Thr Ile Thr Phe Ala His His Arg Val Glu Ile Pro Lys Leu Asn 320 325 330	1072
AAA TTC ATG CAA ACA ATG AAC ACT GCC AAA TAC CCA GTA GAT ATT TCT Lys Phe Met Gln Thr Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser 335 340 345	1120
CAT ACT ATA TTG GAG TGG AAT TAT TTT AAT TGT TCA ATA TCT AAG AAC His Thr Ile Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn 350 355	1168
AGC ATT AGA ATG CAT CAT ATT ACA TTC AAC AAC ACC TTG GAA TGG ACA Ser Ile Arg Met His His Ile Thr Phe Asn Asn Thr Leu Glu Trp Thr 365 370 375	1216
TCA CTG CAC AAC TAT GAT ATG GCG ATG AGT GAT GAA GGT TAC AGT TTA Ser Leu His Asn Tyr Asp Met Ala Met Ser Asp Glu Gly Tyr Ser Leu 380 385 390 395	1264
TAT AAT GCT GTT TAT GCT GTG GCC CAC ACC TAC CAT GAA TAC ATT TTT Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu Tyr Ile Phe 400 405 410	1312
CAA CAA GTA GAG TCT CAG AAA AAG GCA AAA CCC AAA AGA TAT TTC ACT Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Tyr Phe Thr 415 420 425	1360
GCT TGT CAG CAG ATA TGG AAC AGT GTG TGAGGTGTCC AGATGATAAG TATGCCA Ala Cys Gln Gln Ile Trp Asn Ser Val 430 435	1414
ACATAGAGCA AACCCACTGC CTCTCAAGAG CTGTATCATT TCTGGCTTAT GAAGATCCAT	1474
TGGGGATGGC TCTAGGCTGC ATGGCACTGT CCTTCTCGGC CATCACAATT CTAGTCCTCG	1534
TCACATTTGT GAAACACAAC GATACTCCCA TTGTGAAGGC CAATAACCGC ATTCTCAGCT	1594
ACATCCTGCT CATCTCTCTC GTCTTCTGCT TTCTCTGCTC CCTGCTCTTC ATTGGACCTC	1654
CCGACCAGGT CACCTGCATC TTGCAGCAGA CCACATTTGG AGTATTTTTC ACTGTGTCTG	1714
TTTCTACAGT GTTGGCCAAA ACAATAACTG TGGTCATGGC TTTCAAGCTC ACTACTCCAG	1774
GAAGAAGGAT GAGAGGGATG ATGATGACAG GGGCACCTAA GTTGGTCATT CCCATTTGTA	1834
CCCTGATCCA ACTTGTTCTC TGTGGAATCT GGTTGGTCAC ATCTCCTCCC TTTATTGACA	1894
GAGATATACA ATCTGAGCAT GGGAAGATTG TCATTCTTTG CAATAAAGGC TCAGTCATTG	1954
CCTTCCACGT CGTCCTGGGA TACTTGGGCT CCTTGGCTCT GGGGAGCTTC ACTTTGGCTT	2014
TCTTGGCTAG GAACCTTCCT GACACATTCA ATGAAGCCAA GTTCCTAACT TTCAGCATGC TGGTGTTCTG CAGTGTCTGG ATCACCTTCC TCCCTGTCTA CCACAGCACC AGGGGGAGGG	2074 2134
TCATGGTGGT TGTGGAGGTT TTCTCCATCT TGGCTTCTAG TGCAGGGTTG CTAATGTGTA	2134
TCTTTGTCCC AAAGTGTTAT GTTATTTTAA TTAGACCAGA TTCAAATATT ATAAAGAAAC	2254
ATAAAGGTAA AGTGCTTAAT TGAAACTTTC ATGGTATGAA AATGTTAGAT GATATTCAAC	2314
TTATCTTATT CTTCATCTTA ATAAAAGCAG TACTTCATCA TATAAAAAAT AAAGTAATAT	2374
ACAGATTTAT ACTTACAAAC TGGACAGCAA ACATGAATAT GTTGAGAACT GGGATTCTCA	2434
ATTGAGGAAT GGCTACCAAC ATTTTGATCT GTGGTTTTGT GTTTAAGCCA TGCACTTAAT	2494
TAATGATTAA CATGAGGTTA CCCTACTGTC TGTGAACAGC GCCACCTCTA GGCATGCTGT	2554
CCTTGAGTTA TAAGAAAGGG TACTGCATAC ACAATGGACA TGAAGCCAGT AATCAACATT ATTCCACTTG CTTTCATGGA GTTCTTACTT CCAAGTTCAT GCCTTGACTT TATTCAATGT	2614 2674
TCTATGACAA AGGTAGATAA ATAAATAAAC ACTTTCCTCA CAAAAAAAAA AAAAAAAA	2734
	2734

WO 99/00422 PCT/US98/13680 - 98 -

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 436 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Lys Lys Leu Cys Ala Phe Thr Ile Ser Leu Leu Phe Leu Lys Phe Ser Leu Ile Leu Cys Cys Trp Ser Glu Pro Ser Cys Phe Trp Arg Ile Lys Asn Ser Asp Asp Asn Asp Gly Asp Leu Gln Arg Glu Cys His Phe Tyr Leu Gly Ala Ala Asp Thr Pro Val Glu Asp Asn Phe Tyr Ser Ser Leu Leu Lys Phe Arg Ile Ala Ala Ser Glu Tyr Glu Phe Leu Leu Val Met Phe Phe Ala Ile Asp Glu Ile Asn Arg Asn Pro Tyr Leu Leu Pro Asn Ile Thr Leu Met Phe Ser Phe Ile Gly Gly Asn Cys Gln Asp Leu Leu Arg Val Met Asp Gln Ala Tyr Thr Gln Ile Asn Gly His Met Asn Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Ala Ile Gly Leu Thr Gly Pro Ser Trp Lys Thr Ser Leu Lys Leu Ala Met His Ser Ser Met Pro Leu Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu Ser His Gly Met Val Ser Leu Met Phe His Phe Arg Trp Thr Trp Ile Gly Met Val Ile Ser Asp Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr Asp Gln Gln Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly Glu Met Asn Ser Thr Leu Glu Val Ser Phe Arg Arg Trp Glu Glu Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln Trp Asp Val Ile Thr Asn Lys Lys Asp Phe Thr Leu Asn Leu Phe His Gly Thr Ile Thr Phe Ala His His Arg Val Glu Ile Pro Lys Leu Asn Lys Phe Met Gln Thr Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser His Thr Ile Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ile Arg Met His His Ile Thr Phe Asn Asn Thr Leu Glu Trp Thr Ser Leu His Asn Tyr Asp Met Ala Met Ser Asp Glu Gly Tyr Ser Leu Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu Tyr Ile Phe Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Tyr Phe Thr Ala Cys Gln Gln Ile

- 99 -

Trp Asn Ser Val 435

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2732 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA (ix) FEATURE:

- - (A) NAME/KEY: Coding Sequence (B) LOCATION: 80...1375 (D) OTHER INFORMATION: VR10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AGCAGAC ATG AAG	AAG CTC TGT G	A ACGGATTTCA CAACAA CT TTC ACT ATT TCA la Phe Thr Ile Ser 10	TTT 112
ys Phe Ser Leu		T TTG ACT GAA GCA A s Leu Thr Glu Ala S 25	
		r GAT GGA GAT TTG (r Asp Gly Asp Leu (40	
		T AAA CCT ATT GAA 0 p Lys Pro Ile Glu <i>1</i> · 55	
		A TCA GCA AGT GAA 7 e Ser Ala Ser Glu 7	
•		T GAG ATC AAC AAG A p Glu Ile Asn Lys A 90	
eu Pro Asn Ile		C AGC ATC GTT GGT (e Ser Ile Val Gly (105	
 		A TCA TAT ACA CAA A n Ser Tyr Thr Gln 1 120	
 		T TAT TTA GAT GAT T s Tyr Leu Asp Asp S 135	
		A AAA TCC TTA AAA (s Lys Ser Leu Lys 1 0	
 		T GGA CCA TTT AAT (e Gly Pro Phe Asn) , 170	

																_
			GAC Asp 175													640
			CAT His													688
AGA Arg	TGG Trp 205	ACT Thr	TGG Trp	ATA Ile	GGA Gly	CTG Leu 210	GTC Val	ATC Ile	TCA Ser	GAT Asp	GAT Asp 215	GAC Asp	CAG Gln	GGT Gly	ATT Ile	736
CAG Gln 220	TTT Phe	CTC Leu	TCA Ser	GAT Asp	TTA Leu 225	AGA Arg	GAA Glu	GAA Glu	AGC Ser	CAA Gln 230	AGG Arg	CAT His	GGG Gly	ATC Ile	TGT Cys 235	784
TTA Leu	GCT Ala	TTT Phe	GTT Val	AAT Asn 240	ATG Met	ATC Ile	CCA Pro	GAA Glu	AAC Asn 245	ATG Met	CAG Gln	ATA Ile	TAC Tyr	ATG Met 250	ACA Thr	832
			ATA Ile 255													880
			TAT Tyr													928
AGA Arg	TGG Trp 285	GAA Glu	GAT Asp	TTA Leu	GGT Gly	GCT Ala 290	CGG Arg	AGA Arg	ATC Ile	TGG Trp	ATC Ile 295	ACA Thr	ACC Thr	TCA Ser	CAA Gln	976
			ATA Ile													1024
			ACT Thr													1072
			CAA Gln 335													1120
CAT His	ACT Thr	ATA Ile 350	CTG Leu	GAG Glu	TGG Trp	TAA Asn	TAT Tyr 355	TTT Phe	AAT Asn	TGT Cys	TCA Ser	ATC Ile 360	TCT Ser	AAG Lys	AAC Asn	1168
			ATG Met													1216
GCA Ala 380	CTG Leu	CAC His	AAC Asn	TAT Tyr	GAT Asp 385	ATG Met	GCC Ala	ATG Met	AGT Ser	GAT Asp 390	GAA Glu	GGT Gly	TAC Tyr	AAT Asn	TTG Leu 395	1264
TAT Tyr	AAT Asn	GCT Ala	GTT Val	TAT Tyr 400	GTT Val	GCG Ala	GCC Ala	CAC His	ACC Thr 405	TAC Tyr	CAT His	GAA Glu	CAC His	ATT Ile 410	CTT Leu	1312
CAA Gln	CAA Gln	GTA Val	GAG Glu 415	TCT Ser	CAG Gln	AAA Lys	AAG Lys	GTA Val 420	GAA Glu	CAC His	AAC Asn	AGA Arg	TAT Tyr 425	TTC Phe	ACT Thr	1360
GTT	TGT	CAG	CAG	ATA	TAG	AACA	TG :	rgtgi	TAAP	GT C	CAGA:	rgati	A AG	ratgo	CCAA .C	1416

- 101 -

Val Cys Gln Gln Ile 430

ATAGAACAAA CCTACTGCCT CTCAAGAGCT GTATCATTTC TGGCTTTTGA AGAACCACTG 1476 GGGATGGCTC TAGGCTGCAT GGCACTATCC TTCTCGGCCA TCACAATTCT AGTACTAGTC 1536 ACATTTGTGA AGTACAAGAA TACTCCCATT GTGAAGGCCA ATAACCGCAT TCTCAGCTAC 1596 ATCCTGCTCA TCTCTCTAGT CTTCTGTTTT CTCTGCTCCC TGCTCTTCAT TGGACATCCT 1656 GACCAGGTCA CCTGCATCTT GCAGCAGACC ACATTTGGAG TATTTTTCAC TGTGTCTGTT TCTACAGTGT TGGCCAAAAC AATAACTGTG GTCATGGCTT TCAAGTTCAC TACTCCAGGA 1776 AGAAGGATGA GAGGGATGTT GGTAACAGGT GCACCTAAGT TGGTCATTCC CATTTGTACC CTAATCCAAC TTGTTCTCTG TGGAATCTGG TTGGTAACAT CTCCTCCATT TATTGACAGA 1896 GATATACAAT CTGAACATGG GAAGGTAGTC ATTCTTTGCA ATAAAGGCTC TGTCATTGCC TTCCACATTG TCCTGGGATA CTTGGGCTCC TTGGCTCTGG GGAGCTTCAC TTTGGCTTTC 2016 TTGGCTAGGA ACCTTCCTGA CACATTCAAT GAAGCCAAAT TCCTAACTTT CAGCATGCTG 2076 GTGTTCTGCA GTGTCTGGAT CACCTTCCTC CCTGTCTACC ACAGCACCAG GGGGAAGGTC 2136 ATGGTGGTTG TGGAGGTTTT CTCAATCTTG GCTTCTAGTG CAGGGTTGCT AATGTGTATC TTTGTCCCAA AGTGTTATGT TATTTTAGTT AGACCAGATT CAAATTTTAC AAAGAACCGC 2256 AAAGGTAAAT TGCTTTATTG AAATTTTCAT GGTATGAAAA TGTTAGATTA TATTCAACTT 2316 ATCTTATTCT TCATCTTAAC AAAAGTAGTA CTTCATCATA TAAAAAATTA AGTAATATAC 2376 AGATTTATAC TTACAAACTG GACAGCAAAC ATGAATATGT TTAGAACTGG GAATCTCAAT 2436 TGAGGAATGG GTATCATCAT TTTGACCTGT GGTTATGTGT TTAAGCCATG TGTTTAATTA 2496 ATGATTAACA TGAGGTTGCC CTACTGTCTG TGAACCATAC CACCTCTAGG CACACTGTCC 2556 TTGAGTTATA AGATAGGGTA CTGCATACAA AATGGACATG AAACCAGTAA TCAACATTAT CCCTCTTGCT TTCATGGAGT TCTTGCATCC AATTTCATGC CTTGACTTCA TTCAATGTAC 2676

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 432 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Lys Lys Leu Cys Ala Phe Thr Ile Ser Phe Leu Ser Leu Lys Phe 10 Ser Leu Ile Leu Cys Cys Leu Thr Glu Ala Ser Cys Phe Trp Arg Ile 20 25 Lys Asn Ser Glu Asp Ser Asp Gly Asp Leu Gln Arg Glu Cys His Phe 35 40 Tyr Leu Trp Val Ile Asp Lys Pro Ile Glu Asp Asn Phe Tyr Asn Ser 55 Val Leu Asn Phe Arg Ile Ser Ala Ser Glu Tyr Glu Phe Leu Leu Val 70 Met Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu Leu Pro 90 Asn Ile Thr Leu Ile Phe Ser Ile Val Gly Gly His Cys His Asp Leu 100 105 Leu Arg Gly Leu Asp Gln Ser Tyr Thr Gln Ile Asn Gly Arg Val Asn 125 120 Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Asn Ile Gly Leu 130 135 140 Thr Gly Pro Ser Trp Lys Lys Ser Leu Lys Leu Ala Met Asp Ser Ser 150 155 Ile Pro Met Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His 170 175 165 Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu 180 185 190 Ser His Gly Met Val Ser Leu Met Phe Ris Phe Arg Trp Thr Trp Ile · 195 200 205

- 102 -

Gly Leu Val Ile Ser Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp 215 220 Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn 225 230 235 Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr 245 250 Asp Lys Gln Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly 265 260 270 Glu Met Asn Ser Thr Leu Glu Val Ser Phe Arg Arg Trp Glu Asp Leu 275 280 285 Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln Trp Asp Ile Ile Leu 295 300 Asn Lys Lys Glu Phe Thr Leu Asn Leu Phe His Gly Pro Ile Thr Phe 310 315 Ala His His Lys Val Glu Ile Pro Lys Leu Arg Asn Phe Met Gln Thr 325 330 Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser His Thr Ile Leu Glu 340 345 Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ser Lys Met Asp 360 365 Leu Phe Thr Ser Asn Asn Thr Leu Glu Trp Thr Ala Leu His Asn Tyr 375 380 Asp Met Ala Met Ser Asp Glu Gly Tyr Asn Leu Tyr Asn Ala Val Tyr 390 395 Val Ala Ala His Thr Tyr His Glu His Ile Leu Gln Gln Val Glu Ser 405 410 415 Gln Lys Lys Val Glu His Asn Arg Tyr Phe Thr Val Cys Gln Gln Ile 420 · 425 430

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2962 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 81...1601
 - (D) OTHER INFORMATION: VR11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

			ATGI		AC F	TG A	AG A	AG (TC 1	rgt (CT :	TTC I	ACT I	ATT :		60 110
			CTG Leu													158
			TGG Trp 30													206
			TGT Cys													254
GAT	AAT	TTT	TAT	AAT	TCA	GTT	TTA	AAT	TTT	AGA	ATA	TCA	GCA	AGT	GAA .	302

									,								
	Asp	Asn 60	Phe	Tyr	Asn	Ser	Val 65	Leu	Asn	Phe	Arg	Ile 70	Ser	Ala	Ser	Glu	
	TAT Tyr 75	GAG Glu	TTT Phe	CTT Leu	CTG Leu	GTA Val 80	ATG Met	TTT Phe	TTT Phe	GCT Ala	ACT Thr 85	GAT Asp	GAG Glu	ATC Ile	AAC Asn	AAG Lys 90	350
															GTT Val 105		398
															ACA Thr		446
															GAT Asp		494
															TTA Leu		542
															TTT Phe		590
															GTA Val 185		638
															TTT Phe		686
	TTT Phe	AGA Arg	TGG Trp 205	ACT Thr	TGG Trp	ATA Ile	GGA Gly	CTG Leu 210	GTC Val	ATC Ile	TCA Ser	GAT Asp	GAT Asp 215	GAC Asp	CAG Gln	GGT Gly	734
	ATT Ile	CAG Gln 220	TTT Phe	CTC Leu	TCA Ser	GAT Asp	TTA Leu 225	AGA Arg	GAA Glu	GAA Glu	AGC Ser	CAA Gln 230	AGG Arg	CAT His	GGG Gly	ATC Ile	782
															TAC Tyr		830
															GCA Ala 265		878
٠	GTT Val	GTT Val	ATC Ile	ATT Ile 270	TAT Tyr	GGT Gly	GAA Glu	ATG Met	AAC Asn 275	TCT Ser	ACT Thr	CTA Leu	GAA Glu	GTA Val 280	AGC Ser	TTC Phe	926
															ACC Thr		974
															CTC Leu		1022
															AAA Lys	TTA Leu	1070

- 104 -

	315					320					325					330	
•															GAT Asp 345		1118
				_		_									TCT Ser		1166
															GAA Glu		1214
															TAC Tyr		1262
															CAC His		1310
															TAT Tyr 425		1358
															TTT Phe		1406
															CAG Gln		1454
															CTT Leu		1502
															AGT Ser	_	1550
															ACA Thr 505		1598
	ATA Ile	TAG	AACA	GTG :	rgtgi	TAAL	GT C	CAGA!	rgat:	A AG	r at g(CAA	CAT	AGAA	CAA 2	ACCTAC	1657
	ጥርረረ	ուրթար	י ממי	באפרי	יעידיטין	יי אי	بالمليط	יים	de aberto	ኮር፤ አ አ 4	ממב	CNC	rece	ייימבי	تاتاتات	CTAGGC	1717
																AAGTAC	1777
																ATCTCT	1837
									-							ACCTGC	1897
							_									TTGGCC AGAGGG	1957 2017
									_							CTTGTT	2017
																TCTGAA	2137
																GTCCTG	2197
									-							AACCTT	2257
																AGTGTC GTGGAG	2317 2377
																AAGTGT	2437
																TTGCTT	2497
																TTCATC	2557

TTAACAAAAG	TAGTACTTCA	TCATATAAAA	AATTAAGTAA	TATACAGATT	TATACTTACA	2617
AACTGGACAG	CAAACATGAA	TATGTTTAGA	ACTGGGAATC	TCAATTGAGG	AATGGGTATC	2677
ATCATTTTGA	CCTGTGGTTA	TGTGTTTAAG	CCATGTGTTT	AATTAATGAT	TAACATGAGG	2737
TTGCCCTACT	GTCTGTGAAC	CATACCACCT	CTAGGCACAC	TGTCCTTGAG	TTATAAGATA	2797
GGGTACTGCA	TACAAAATGG	ACATGAAACC	AGTAATCAAC	ATTATCCCTC	TTGCTTTCAT	2857
GGAGTTCTTG	CATCCAATTT	CATGCCTTGA	CTTCATTCAA	TGTACTATGA	CAAAGGTACA	2917
TAAATAAATA	AACACTTTCC	CCACAAAAAA	ааааааааа	AAAAA		2962

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 507 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Lys Lys Leu Cys Ala Phe Thr Ile Ser Phe Leu Ser Leu Lys Phe 10 Ser Leu Ile Leu Cys Cys Leu Thr Glu Ala Ser Cys Phe Trp Arg Ile 20 25 Lys Asn Ser Glu Asp Ser Asp Gly Asp Leu Gln Arg Glu Cys His Phe 35 40 Tyr Leu Trp Val Ile Asp Lys Pro Ile Glu Asp Asn Phe Tyr Asn Ser 55 60 Val Leu Asn Phe Arg Ile Ser Ala Ser Glu Tyr Glu Phe Leu Leu Val 75 70 Met Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu Leu Pro 90 Asn Ile Thr Leu Ile Phe Ser Ile Val Gly Gly His Cys His Asp Leu 100 105 110 Leu Arg Gly Leu Asp Gln Ser Tyr Thr Gln Ile Asn Gly Arg Val Asn 120 115 Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Asn Ile Gly Leu 135 140 Thr Gly Pro Ser Trp Lys Lys Ser Leu Lys Leu Ala Met Asp Ser Ser 150 155 Ile Pro Met Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His 165 170 Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu 180 185 190 Ser His Gly Met Val Ser Leu Met Phe His Phe Arg Trp Thr Trp Ile 200 205 195 Gly Leu Val Ile Ser Asp Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp 220 215 Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn 230 235 Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr 245 250 Asp Lys Gln Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly 260 265 270 Glu Met Asn Ser Thr Leu Glu Val Ser Phe Arg Arg Trp Glu Asp Leu 280 285 Gly Ala Arg Arg Ile Trp Ile Thr Thr Ser Gln Trp Asp Ile Ile Leu 295 300 Asn Lys Lys Glu Phe Thr Leu Asn Leu Phe His Gly Pro Ile Thr Phe 310 315 Ala His His Lys Val Glu Ile Pro Lys Leu Arg Asn Phe Met Gln Thr 330 325 Met Asn Thr Ala Lys Tyr Pro Val Asp Ile Ser His Thr Ile Leu Glu 340

348

Trp Asn Tyr Phe Asn Cys Ser Ile Ser Lys Asn Ser Ser Lys Met Asp 365 355 360 Leu Phe Thr Ser Asn Asn Thr Leu Glu Trp Thr Ala Leu His Asn Tyr 375 380 370 Asp Met Ala Met Ser Asp Glu Gly Tyr Asn Leu Tyr Asn Ala Val Tyr 385 390 395 400 Val Ala Ala His Thr Tyr His Glu His Ile Leu Gln Gln Val Glu Ser 405 410 415 Gln Lys Lys Val Glu His Asn Arg Tyr Phe Thr Val Cys Gln Gln Val 420 425 430 Ser Ser Leu Met Lys Thr Arg Val Phe Thr Asn Pro Val Gly Glu Leu 440 Val Asn Met Lys His Arg Glu Asn Gln Cys Thr Glu Tyr Asp Ile Phe 455 Ile Ile Trp Asn Phe Pro Gln Gly Leu Gly Leu Lys Leu Lys Ile Gly 470 475 Ser Tyr Ile Pro Cys Phe Pro Lys Ser Gln Gln Leu His Ile Ser Asp 485 490 Asp Leu Glu Trp Ala Met Gly Gly Thr Ser Ile 505 500

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2821 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 60...992

70

(D) OTHER INFORMATION: VR12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

,						
GACGTTTTT	C TGCATCAGAA A	ACGGATTTCA (CAGCAGCTCC .	ATCTCAGATC (CTAGCAGAC	A 60 Me
	GC TCT GCA CTT Leu Cys Thr I 5				ys Phe Se	108
	CT TGT GCT GT Leu Cys Cys 1 20					156
	TG AAG ATA ATO Glu Asp Asn A					204
	GA AAA CTG ATG Lys Thr Asp (r Phe Tyr A		252
	TT TTA GAA TTO Phe Arg Ile 1	Ala Gly Ser	Glu Tyr Gl		eu Val Me	300

TGT TTT TTG CTA CTG ATG AGA TCA AGA ATC CTT ATC TTT TAC CCA t Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu Leu Pro As.

75

	85	90	95	i	
	Met Phe Ser	A TCA TTG GTG G Ile Ile Gly Gly 105			396
		T ATG CAC AAA T Tyr Ala Gln Ile 120			444
		T TAG ATG ATT C Leu Asp Asp Ser			492
		T CCT TAA AAC T Ser Leu Lys Leu 155	Ala Met His Se		540
		AC CAT TTA ATC C Pro Phe Asn Pro 170		p His As	588
	His Val His	CC AGG TAG CCC C Gln Val Ala Pro 185			636
		SA TGT TTC ATT T Met Phe His Phe 200			684
		TG ATC AGG GTA T Asp Gln Gly Ile			732
		GC ATG GGA TCT G His Gly Ile Cys 235	Leu Ala Phe Va		780
		SA TAT ACA TGA C Ile Tyr Met Thr 250	Arg Ala Thr I		828
· · · · · · · · · · · · · · · · · · ·	e Met Thr Ser	TT CAG CAA AGG T Ser Ala Lys Val 265			876
		AG CAA GCT TTA G Ala Ser Phe Arg 280			924
		CA CAA CCA CAC A Thr Thr Thr Glr			972
	GAC TTC ACC C G Leu His Pro 310	r taatctcttc cai	GGGACTA TTACTT	TTGC ACACC 1	027
ACAAAGATGA GA	ATTCCTAAA TTT	AGGAATT TTATGCA	AC AAAGAAAACT	CCAAATACC	108
TTGTAGATAT T	CTCATACT ATT	TTGGAGT GGAATTAT	TT TAATTGTTCA	ATCTCTAAGA	114
		ACATTCA ACAACACA			120
		GAAGGTT ACAATTTO			126
		CTTCAAC AAGTAGAG CAGGTTC CCTCCTCT			132°
		AAAGAAA CGGCAGAT		• •	144

GCCTAGAAAA TGAGGTTTCC AATGAAACAG ATATGGAACA GTGTGTGAGA TGTCCAGATA ATAAATATGC CAATTTAGAG CAAACCCACT GCCTCCAAAG AACGGTGTCA TTTCTGGCTT ATGAAGATCC ATTGGGGATG GCTCTAGGCT GCATGGCACT GTCCTTCTCG GCCATCACAA 1627 TTCTAGTCCT CGTCACATTT GTGAAGTACA AGGATACTCC CATTGTGAAG GCCAATAACC GCATTCTCAG CTACATCCTG CTCATCTCTC TCGTCTTCTG CTTTCTCTGT TCCCTGCTCT 1747 TCATTGGACA TCCCGACCAG GTCACCTGCA TCTTGCAGCA GACCACATTT GGAGTATTGT TCACTGTGTC TGTTTCTACA GTGTTGGCCA AAACAATAAC TGTGGTCATG GCTTTCAAGC 1867 TCACTACTCC AGGAAGAAGG ATGAGAGGGA TGATGATGAC AGGGGCACCT AAGTTGGTCA 1927 TTCCCATTTG TACCCTGATC CAACTTGTTC TCTGTGGAAT CTGGTTGGTC ACATCTCCTC 1987 CCTTTATTGA CAGAGATATA CAATCTGAAC ATGGGAAGAT TGTCATTCTT TGCAATAAAG GCTCTGTCGT TGCCTTCCAC GTCGTCCTGG GATACTTGGG CTCCTTGGCT CTGGGGAGCT 2107 TCACTTTGGC TTTCTTGGCT AGGAACCTTC CTGACACATT CAATGAAGCC AAGTTCCTAA 2167 CTTTCAGCAT GCTGGTGTTC TGCAGTGTCT GGATCACCTT CCTCCCTGTC TACCACAGCA 2227 CCAGGGGGAA GGTCATGGTG GTTGTGGAGG TTTTCTCCAT CTTGGCTTCT AGTGCAGGGT TGCTAATGTG TATCTTTGTC CCAAAGTGTT ATGTTATTTT AATTAGACCA GATTCAAATT TTATACAGAA CCACAAAGGT AAATTGCTTT ATTGAAACTT TCATGGTATG AAAATGTTAG 2407 ATGATATTCA ACTTATCTTA TTCTTCATCT TAATAAAAGC AGTACTTCAT CATATAAAAA ATAAAGTAAT ATACAGATTT ATACTTACAA ACTGGACAGC AAACATGAAT ATGTTGAGAA 2527 CTGGGATTCT CAATTGAGGA ATGGCTACCA ATATTTTGAT CTGTGGTTTT GTGTTTAAGC CATGTACTTA ATTAATGATT AACATGAGGT TACCCTACTG TCTTTGAACA GCGCCACCTC 2647 TAGGCATGCT GTCCTTGAGT TATAAGAAAG GGTACTGCAT ACACAATGGA CATGAAGCCA GTAATCAACA TTATTCCACT TGCTTTCATG GAGTTCTTAC TTCCAAGTTC ATGCCTTGAC 2767 TTTATTCAAT GTTCTATGAC AAAGGTAGAA TAAATAAATA AACACTTTCC TCAC

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 311 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Lys Gln Leu Cys Thr Phe Thr Ile Ser Leu Leu Phe Leu Lys Phe 10 Ser Leu Ile Leu Cys Cys Trp Ser Glu Pro Ser Cys Phe Trp Arg Ile 20 25 Lys Lys Ser Glu Asp Asn Asp Gly Asp Leu Gln Arg Glu Cys His Phe 40 Tyr Leu Trp Lys Thr Asp Glu Pro Ile Glu Asp Ser Phe Tyr Asn Tyr 55 Asp Leu Ser Phe Arg Ile Ala Gly Ser Glu Tyr Glu Leu Leu Leu Val Met Phe Phe Ala Thr Asp Glu Ile Asn Lys Asn Pro Tyr Leu Leu Pro 90 Asn Met Ser Leu Met Phe Ser Ile Ile Gly Gly Asn Cys His Asp Leu 100 105 110 Leu Arg Ser Leu Asp Gln Glu Tyr Ala Gln Ile Asp Gly His Met Asn 115 120 125 120 Phe Val Asn Tyr Phe Cys Tyr Leu Asp Asp Ser Cys Ala Thr Gly Leu 135 140 Thr Gly Pro Ser Trp Lys Thr Ser Leu Lys Leu Ala Met His Ser Ser 150 155 Met Pro Leu Val Phe Phe Gly Pro Phe Asn Pro Asn Leu Arg Asp His 165 170 175 Asp Arg Leu Pro His Val His Gln Val Ala Pro Lys Asp Thr His Leu 180 185 190
Ser His Gly Met Val Ser Leu Met Phe His Phe Arg Trp Thr Trp Ile 200 205 Gly Leu Val Ile Ser Asp Asp Asp Gln Gly Ile Gln Phe Leu Ser Asp 215 220

- 109 -

WO 99/00422 PCT/US98/13680

Leu Arg Glu Glu Ser Gln Arg His Gly Ile Cys Leu Ala Phe Val Asn 230 235 Met Ile Pro Glu Asn Met Gln Ile Tyr Met Thr Arg Ala Thr Ile Tyr · 245 250 Asp Thr Gln Ile Met Thr Ser Ser Ala Lys Val Val Ile Ile Tyr Gly 265 270 Asp Met Asn Ser Thr Leu Glu Ala Ser Phe Arg Arg Trp Glu Glu Leu 280 285 Gly Ala Arg Arg Ile Trp Ile Thr Thr Gln Trp Asp Val Ile Thr 295 300 Asn Lys Lys Arg Leu His Pro 305

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2773 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence (B) LOCATION: 3...1238

 - (D) OTHER INFORMATION: VR13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

	GAA GAT AAT GAS Glu Asp Asn Asp	
	GG GCA GTT GAT A Y Ala Val Asp Ly 30	ys Pro
	 AG TTT AGA ATT GO os Phe Arg Ile A 45	
Phe Leu Leu	TT GCT ACT GAT G ne Ala Thr Asp G 60	
	 CT TTG ATG TTC TO ir Leu Met Phe So 75	
	GT TTG GAT CAA G Ly Leu Asp Gln A	
	AT TAT TTC TGT TO Sn Tyr Phe Cys T	
Ala Ile Gly	CA TCA TGG AAA AG TO Ser Trp Lys T 125	
	TG GTT TTC TTT Go	

- 110 -

	•											
		130			135			140				
TTT Phe											479	€
GTA Val 160											521	7
TTT Phe											57!	5
AAG Lys											62:	3
GGG Gly											67:	L
TAC Tyr											71	9
GCA Ala 240						_			_	_	76	7
AGC Ser											81	5
ACC Thr											86	3
CTC Leu			ACT Thr								91	1
AAA Lys										GTA Val	95	9
			ACT Thr								100	7
			AGT Ser 340								105	5
			CTG Leu				_		_	_	110	3
			AAT Asn								115	1
His										AGA Arg	119	9

WO 99/00422 PCT/US98/13680 - 111 -

TTT TTC ACT GTT TGT CAG CAG CAG ATA TGG AAC AGT GTG TGAAGTGTCC AT 1250 Phe Phe Thr Val Cys Gln Gln Gln Ile Trp Asn Ser Val ATGATAAGTA TGCCAACATA GAGAAAACCC ACTGCCTCTC AAGAGCTGTA TCATTTCTGG CTTATGAAGA TCCATTGGGG ATAGCTCTAG GCTGCATAGC ACTGTCCTTC TCAGCCATCA CAATTCTAGT ACTAATCACA TTTTTGAAGT ACAAGGATAC TCCCATTGTG AAGGCCAATA 1430 ACCGCATTCT CAGCTACATC CTGCTCATCT CTCTAGTCTT CTGCTTTCTC TGCTCCCTGC 1490 TCTTCATTGG ACATCCAAAC CAGGTCTCCT GCGTCTTGCA GCAGACCACA TTTGGAGTAT 1550 TTTTCACTGT GTCTGTTTCT ACAGTGTTGG CCAAAACAAT AACTGTGGTC ATGGCTTTCA 1610 AGCTCACTAC TCCAGGAAGA AGAATGAGAG AGATGTTGGT AACAGGGGCA CCTAAGTTGG 1670 TCATTCCCAT TTGTACCCTA ATCCAATTTG TTCTCTGTGG AATCTGGTTG ATAACATCTC 1730 CTCCATTTAT TGACAGAGAT ATACAATCTG AGCATGGGAA GATTGTCATT CTTTGCAATA AAGGCTCTGT CATTGCCTTC CATGTTGTCC TGGGATACTT GGGCTCCTTG GCTCTGGGGA 1850 GCTTCACTTT GGCTTTCTTG GCTAGGAACC TTCCTGACAC ATTCAATGAA GCCAAATTCC TGACTTTCAG CATGCTGGTG TTCTGCAGTG TCTGGATCAC CTTTCTCCCT GTCTACCATA 1970 GCACCAGGGG GAAGGTCATG GTGGTTGTGG AGGTTTTCTC AATCTTGGCT TCTAGTGCAG 2030 2090 ATTTTATACG GAAGTACAAA GATAAATTTC GTTATTGAAA TATTCATACT ATGAAAATGT TAGATTATAC TCAACATATT TTTCTTTGTC TTAACAAAAG TAGTACTTAA TCTTATAAAA 2210 ATTTAAATAA TATACAAATT TGAACTTACA AACAGGACAG AACTGTCTAT TGTAATACCA 2270 ATTACAAAAC TTTGGTGAAA AATGGTCTCA TTCATAAGGA CACAATTCTG AAGATATTGA 2330 GAACCAGGAA TCTCAACTGC GGAAACGCTA CCATCATCCT GACCTGTGGT TTTGTGTGTA AAGCATGAAC TTAATTAATG ATTAATATAA GGTGACCATA CTGACTGTGA ACACTACCAT 2450 CTCTGGGCAA GTTGTTCTTG TAGTTGTAAG AAAAAGCTCT GAAGACAACA TGGAAGTAAA GCCAGTAATC ACCATTATCC CTCATGCTTT CATGGAGTGG CTGCATCCAA TTTCATGCCT 2510 2570 TGGCTTCATT CAATATACTG TGACCAAGGT ACATAAGTAA AGAAACACTT TTCTTACAAG 2630 GTATTTTTAC ATCAACGGAA TTTAAAATAT CAACAAAATG GTAAATTGTT TCTGTTGAGA 2750

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 412 amino acids
 - (B) TYPE: amino acid

TTTAGAATAT CATCGATTCC TGA

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Ala Ser Cys Phe Trp Arg Ile Lys Asn Ser Glu Asp Asn Asp Gly Asp 10 Leu Gln Arg Glu Cys His Phe Tyr Leu Gly Ala Val Asp Lys Pro Ile 20 25 30 Glu Asp Asn Phe Tyr Asn Ser Leu Leu Lys Phe Arg Ile Ala Ala Ser 35 40 Glu Tyr Glu Phe Leu Leu Val Met Phe Phe Ala Thr Asp Glu Ile Asn 55 60 Lys Asn Pro Tyr Leu Leu Pro Asn Ile Thr Leu Met Phe Ser Ile Ile 70 75 Gly Gly Asn Cys His Asp Leu Leu Arg Gly Leu Asp Gln Ala Tyr Thr 90 85 Gln Ile Asn Gly His Met Asn Phe Val Asn Tyr Phe Cys Tyr Leu Asp 100 105 Asp Ser Cys Ala Ile Gly Leu Thr Gly Pro Ser Trp Lys Thr Ser Leu 120 125 Lys Leu Ala Met His Ser Ser Met Pro Leu Val Phe Phe Gly Ser Phe 135 140 Asn Pro Asn Leu His Asp His Asp Arg Leu His His Val His Gln Val 150 155 Ala Thr Lys Asp Thr His Leu Ser His Gly Ile Val Ser Leu Met Phe .

- 112 -

170 His Phe Arg Trp Thr Trp Ile Gly Leu Val Ile Ser Asp Asp Asp Lys 180 185 190 Gly Ile Gln Phe Leu Ser Asp Leu Arg Glu Glu Ser Gln Arg His Gly 195 200 205 Ile Cys Leu Ala Phe Val Asn Met Ile Pro Glu Asn Met Gln Ile Tyr 210 215 220 Met Thr Arg Ala Thr Ile Tyr Asp Lys Gln Ile Met Thr Ser Leu Ala 230 235 Lys Val Val Ile Ile Tyr Gly Glu Met Asn Ser Thr Leu Glu Val Ser 245 250 255 Phe Arg Arg Trp Glu Asn Leu Gly Ala Arg Arg Ile Trp Ile Thr Thr 260 265 270 Ser Gln Trp Asp Val Ile Thr Asn Lys Lys Glu Phe Thr Leu Asn Leu 280 275 285 Phe His Gly Thr Ile Thr Phe Ala His Arg Arg Phe Glu Ile Pro Lys 290 295 300 Phe Lys Lys Phe Met Gln Thr Met Asn Thr Ala Lys Tyr Pro Val Asp 310 315 Ile Ser His Thr Ile Leu Glu Trp Asn Tyr Phe Asn Cys Ser Ile Ser 325 330 335 Lys Asn Ser Ser Lys Met Asp His Ile Thr Phe Asn Asn Thr Leu Glu 340 345 Trp Thr Ala Leu His Asn Tyr Asp Met Val Met Ser Asp Glu Gly Tyr 355 360 365 Asn Leu Tyr Asn Ala Val Tyr Ala Val Ala His Thr Tyr His Glu His 375 380 Ile Phe Gln Gln Val Glu Ser Gln Lys Lys Ala Lys Pro Lys Arg Phe 390 395 Phe Thr Val Cys Gln Gln Gln Ile Trp Asn Ser Val 410

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3108 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULF TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 116...2527
 - (D) OTHER INFORMATION: VR14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

 		SATGTG S ATG Met 1	60 118						
 	CTC Leu		166						
 	GAT Asp		214						
				 		 	GCA Ala		262

- 113 -

35			40			45				
	ACA Thr									310
	ACA Thr									358
	GAA Glu									406
 	AGA Arg 100				 		_	 		454
	TAT Tyr									502
	AAT Asn									550
	GTA Val									598
	ATC Ile									646
	GAA Glu 180									694
	GCA Ala									742
	GGC Gly									790
	TTG Leu									838
	ATG Met							Thr	GAA Glu	886
	TAC Tyr 260									934
	GAA Glu								GAA Glu	982
	ATT Ile								TTC Phe 305	1030

								-								-
	ACC Thr															1078
	TTT Phe															1126
	ACA Thr															1174
	TGG Trp 355															1222
	AAG Lys															1270
	TTT Phe															1318
	CAT His															1366
Asp	AAT Asn	Gln 420	Ala	Ile	Asp	Asn	Gly 425	Lys	Lys	Glu	Pro	Ser 430	Ser	Ser	His	1414
	Leu 435	Lys														1462
	GGG															1510
	Asp															1558
	AAG Lys	Leu		Lys	Phe	Ser	Pro	Tyr	Leu	Pro		Gly	Arg	His		1606
	TTA Leu		Val													1654
	TCC Ser 515						Asp									1702
	AAG Lys										Cys					1750
Glı	AAT Asn	Glu	Ile	Ser 550	Asn	Glu	Thr	Thr	Val 555	Val	Leu	Сув	Val	Phe 560	Val	1798
AA	CAT	CAT	GAC	ACT	CCT	ATT	GTG	AAG	GCC	AAT	AAC	AGA	AGC	CTC	AGC	. 1846

																-
Lys	His	His	Asp 565	Thr	Pro	Ile	Val	Lys 570	Ala	Asn	Asn	Arg	Ser 575	Leu	Ser	
			CTC Leu													1894
			CTT Leu													1942
			GTA Val													1990
			GTT Val													2038
			CTG Leu 645													2086
			CAA Gln			Leu										2134
			GAT Asp													2182
			AAG Lys													2230
			CTG Leu													2278
			GAC Asp 725													2326
			TGT Cys													2374
			AAA Lys													2422
			GGG Gly													2470
			AGA Arg												AAA Lys	2518
		TTC Phe		ACAA	ATA :	ATTI	GGAA'	TT C	rgtc:	AAAT(G TA	AAGT"	rggt	ACA'	TACCCA	2576
															GCTCTA TTGTAC	2636 2696

TCATTCACTT	TCTTCATTTT	CTCTCAGAGA	ACTAAACTCT	CTAATTATTA	CAATTTTATT	2756
CTTCATTTTG	CTTTCATGGA	GATTGCCCTC	TGGTAACTTC	CAAAAAATGT	TGATAAGGCA	2816
GTTGAATCCA	CCACTTTGTG	TAGAAAAATG	AGATCTAGGA	AGACAGGGTT	ACACATAAAA	2876
ACCATCTACC	AAAATAAATA	ATCAATGAGA	AACACAGACT	AACTAAATAA	TCAGCAAAGA	2936
TGAAATCAGA	ACATATTTTC	TAATTTCCAG	TAAGAGCACA	CACATAAGAA	AATACTTACT	2996
TTTTTCATCT	GTTCTTCAAT	CTACTGGCCA	ATAGTCTAAG	GAGGAAATGT	TCCTTTTCTG	3056
CTGTCAAATA	TTATATAAAA	ATATCCAAAA	AAAAAAAAA	AAAAAAAAA	AA	3108

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 804 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Phe Ile Phe Met Glu Val Phe Phe Leu Leu Asn Ile Thr Leu Leu 5 10 Met Ala Asn Phe Ile Asp Pro Arg Cys Phe Trp Arg Ile Asn Leu Asp 20 25 Glu Ile Met Asp Glu Tyr Leu Gly Leu Ser Cys Ala Phe Ile Leu Ala 40 45 Ala Val Gln Thr Pro Ile Glu Asn Asp Tyr Phe Asn Lys Thr Leu Asn 55 60 Val Leu Lys Thr Thr Lys Asn His Lys Tyr Ala Leu Ala Leu Val Phe 70 75 Ala Met Asp Glu Ile Asn Arg Asn Pro Asp Leu Leu Pro Asn Met Ser 90 Leu Ile Ile Arg Tyr Thr Leu Gly Arg Cys Asp Gly Lys Thr Val Ile 100 105 Pro Thr Pro Tyr Leu Phe Arg Lys Lys Lys Glu Ser Pro Ile Pro Asn 120 115 Tyr Phe Cys Asn Glu Glu Thr Met Cys Ser Tyr Leu Leu Thr Gly Pro 135 140 His Trp Glu Val Ser Leu Gly Phe Trp Lys His Met Asn Ser Phe Leu 150 155 Ser Pro Arg Ile Leu Gln Leu Thr Tyr Gly Pro Phe His Ser Ile Phe 170 175 165 Ser Asp Asp Glu Gln Tyr Pro Tyr Leu Tyr Gln Met Ala Pro Lys Asp 185 190 180 Thr Ser Leu Ala Leu Ala Met Val Ser Phe Ile Leu Tyr Phe Ser Trp 195 200 205 Asn Trp Ile Gly Leu Val Ile Pro Asp Asp Asp Gln Gly Asn Gln Phe 215 220 210 Leu Leu Glu Leu Lys Lys Gln Ser Glu Asn Lys Glu Ile Cys Phe Ala 230 235 Phe Val Lys Met Ile Ser Val Asp Asp Val Ser Phe Pro Gln Asn Thr 245 250 Glu Met Tyr Tyr Asn Gln Ile Val Met Ser Ser Thr Asn Val Ile Ile 265 270 260 Ile Tyr Gly Glu Thr Tyr Asn Phe Ile Asp Leu Ile Phe Arg Met Trp 275 280 Glu Pro Pro Ile Leu Gln Arg Ile Trp Ile Thr Thr Lys Gln Leu Asn 295 300 Phe Pro Thr Arg Lys Lys Asp Ile Ser His Gly Thr Phe Tyr Gly Ser 310 315 Leu Thr Phe Leu Pro His His Gly Val Ile Ser Gly Phe Lys Asn Phe 325 330 Val Gln Thr Trp Phe His Leu Arg Asn Thr Asp Leu Tyr Leu Val Met 340 345

- 117 -Gln Glu Trp Lys Tyr Phe Asn Tyr Glu Asp Ser Ala Ser Thr Cys Lys Ile Leu Lys Asn Asn Ser Ser Asn Ala Ser Phe Asp Trp Leu Met Glu Gln Lys Phe Asp Met Thr Phe Ser Glu Asn Ser His Asn Ile Tyr Asn Ala Val His Ala Ile Ala His Ala Leu His Glu Met Asn Leu Gln Gln Ala Asp Asn Gln Ala Ile Asp Asn Gly Lys Lys Glu Pro Ser Ser Ser His Cys Leu Lys Val Asn Ser Phe Leu Arg Arg Ile Tyr Phe Thr Asn Pro Pro Gly Asp Lys Val Phe Met Lys Gln Arg Val Ile Met His Asp Glu Tyr Asp Ile Val His Phe Val Asn Leu Ser Gln His Leu Gly Ile Lys Met Lys Leu Gly Lys Phe Ser Pro Tyr Leu Pro His Gly Arg His Ser His Leu Tyr Val Asp Arg Ile Glu Leu Ala Thr Gly Arg Arg Lys Met Pro Ser Ser Val Cys Ser Ala Asp Cys Ser Pro Gly Phe Arg Arg Leu Trp Lys Glu Gly Met Ala Ala Cys Cys Phe Val Cys Ser Pro Cys Pro Glu Asn Glu Ile Ser Asn Glu Thr Thr Val Val Leu Cys Val Phe Val Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ser Leu Ser Tyr Leu Leu Met Ser Leu Met Ser Cys Phe Leu Cys Ser Phe Phe Phe Ile Gly Leu Pro Asn Arg Ala Ile Cys Val Leu Gln Gln Ile Thr Phe Gly Ile Val Phe Thr Met Ala Val Ser Thr Val Leu Ala Lys Thr Val Thr Val Val Leu Ala Phe Lys Val Thr Asp Pro Gly Arg Arg Leu Arg Asn Phe Leu Val Ser Gly Thr Pro Asn Tyr Ile Ile Pro Ile Cys Ser Leu Leu Gln Cys Val Leu Cys Ala Ile Trp Leu Ala Val Ser Pro Pro Phe Val Asp Ile Asp Glu His Thr Leu His Gly His Ile Ile Ile Val Cys Asn Lys Gly Ser Val Thr Ala Phe Tyr Cys Ile Leu Gly Tyr Leu Ala Cys Leu Ala Leu Gly Asn Phe Ser Val Ala Phe Leu Ala Lys Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys His Met Val Ala Val Glu Ile Phe Ser Ile Leu Ala Ser Ser Ala Gly Ile Leu Gly Cys Ile Phe Val Pro Lys Ile Tyr Ile Ile Leu Met Arg Pro Glu Arg Asn Ser Thr Gln Lys Ile Arg Glu

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3689 base pairs

(B) TYPE: nucleic acid

Lys Ser Tyr Phe

(C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
 (ix) FEATURE:
- - (A) NAME/KEY: Coding Sequence (B) LOCATION: 39...419 (D) OTHER INFORMATION: VR15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
TCAAAATCCG CACTGCCCAA GTTTAAGGCA GGAAAAAT ATG TTC ATT TTC ATG GGA Met Phe Ile Phe Met Gly 1 5	56
GTC TTC TTC CTC CTT AAT ATT ACA CTT CTC ATG GCC AAT TTC ATT AAT Val Phe Phe Leu Leu Asn Ile Thr Leu Leu Met Ala Asn Phe Ile Asn 10 15 20	104
CCC AGG TGC TTT TGG AGA ATA AAT TTG GAT GAA ATA ACG GAT GAA TAT Pro Arg Cys Phe Trp Arg Ile Asn Leu Asp Glu Ile Thr Asp Glu Tyr 25 30 35	152
TTG GGA TTA TCT TGT ACT TTC ATC CTG GCG GCA GTT CAG ACA CCC ACT Leu Gly Leu Ser Cys Thr Phe Ile Leu Ala Ala Val Gln Thr Pro Thr 40 50	200
GAA AAA GAT TAT TTC AAC AAG ACT CTT AAT GTT CTA AAA ACA ACT AAA Glu Lys Asp Tyr Phe Asn Lys Thr Leu Asn Val Leu Lys Thr Thr Lys 60 65 70	248
AAC CAC AAA TAT GCT TTG GCA TTG GTG TTT GCA ATG GAT GAA ATC AAC Asn His Lys Tyr Ala Leu Ala Leu Val Phe Ala Met Asp Glu Ile Asn 75 80 85	296
AGA AAT CCT GAT CTT TTA CCA AAT ATG TCT TTG ATT ATA AGA TAC ACT Arg Asn Pro Asp Leu Leu Pro Asn Met Ser Leu Ile Ile Arg Tyr Thr 90 95 100	344
TTG GGC CTT TGT GAT GGA AAA ACT GTA ACA CCT ACA CCA TAT TTA TTT Leu Gly Leu Cys Asp Gly Lys Thr Val Thr Pro Thr Pro Tyr Leu Phe 105 110	392
CAT AAA AAA AAA ACA AAG CCC TAT CCC TAATTATTTC TGTAATGAAG AGACTAT His Lys Lys Lys Thr Lys Pro Tyr Pro 120	446
GTGTTCATTT CTGCTTTCAG GACCCAAGTG GGATGTATCT TTAAGTTTCT GGATGTACCT	506
GGACAGCTTC TTATCTCCGC GTATCCTTCA GCTTACCTAT GGACCTTTCC ATTCTATCTT	566 626
CAGTGATGAT GAACAATATC CCTATCTCTA TCAGATGGCC CCAAAGGACA CATCTCTAGC ATTGGCAATG GTCTCCTTCA TACTTTATTT GAAATGGAAC TGGATTGGCC TTGTCATCCC	686
AGATGACGAT CAAGGAAACC AATTTCTTTT AGAGTTGAAG AAACAGAGTG AAAACAAGGA	746
AATTTGCTTT GCCTTTGTGA AAATGATCTC TGTTGATGAT ACTTCATTTC CACATAAAAC	806
TGAAATGGAC TACAACCAAA TTGTGATGTC ATCCACAAAT GTTATTATCA TTTATGGAGA AACACGCAAT TTCATTTATT TGATCTTCAG AATGTGGGAA CCTCCCATTT TACAGAGAAT	866 926
AACACGCAAT TTCATTTATT TGATCTTCAG AATGTGGGAA CCTCCCATTT TACAGAGAAT ATGGATCACC ACAAAACAAT TGAATTTCCC TACCAGGAAG ACAGACATAA GTCATGGCAC	986
ATTCTATGGA TCACTTACTT TTCTACCCCA CCATGGTGAG ATTTCTGGCT TTAAAAAGTT	1046
TGTACAGACA TGGTTCCATG TCAGAAACAC AGATTTATAT TTAGTAATGC CAGAGTGGAA	1106
CTATTTTAAC TATGTAAGCT CAGCATCCAA TTGTAAAATA CTGAAGAACA ATTCATCTGA	1166 1226
TGCCTCATTT GATTGGCTAA TGGAACAGAA GTTTGACATG ACCTTTAGTG AGAATAGTCA TAACATATAC AATGCTGTGC ATGCCATAGC CCATGCCCTC CATGAGATGA ATCTGCAACA	1226
GGCTGATAAT CAGGCAATAG GCAATGGAAA AGGAGCCAGT TCTCACTGCT TGAAGGTAAA	1346
CTCCTTTCTA AGAAGGACCT ACTTCACTAA TCCTCTTGGG GACAAAGTGT TTATGAAGCA	1406
AAGAGTAATA ATGCAGGATG AATATGATAT TATTCACTTT GGGAATCTCT CACAACACCT	1466

- 119 -

TGGGATTAAG ATGAAGTTAG GAAAGTTCAG CCCATATTTA CCACATGGTC GACACTCTCA CTTATATGTA GACATGATTG AGTTGGCCAC AGGAAGAAGA AAGATGCCAT CCTCTGTGTG 1586 CAGTGCAGAT TGTAGTCCTG GATTCAGAAG ATTGTGGAAG GAGGGAATGG CAGCCTGCTG TTTTGTTTGC AGCCCCTGCC CAGAAAATGA AATTTCTAAT GAGACAAGCT CCTCTCCATT 1706 TCATCCTTGC ATTCAGACAG GAACAATTAT GGGCTGGAGA TGTGACTATG GGATGGGAAT 1766 CCCATCACTC ACTTGATGTC CTGTCTTCCG GCTGGAGGTG GGCTCTTTAA GTTAACACTA TCTACTGTAG TACATTTCAT CTAAGGTCTC TGACCTCCCA AGTCTCTGGT GCATTTTGGT GGGTCCACCC ACCCTCCTAT TACCTGAAGT TGCCTGTTTA TATTCTTTTT GCTGGTCCTC AGAGATCGGT TCCCCTCTCA CCTGCCCACA CACCACAAAC CCCTTTCAAA TAACATCATA 2006 AATGATACAA TGAAGTTAAG TATACAAAGA ACAAATTGCT TGGTTTTATT TCATTTAAAT CTTTATGAAC TTTATGAATT GAAATCAATG CTCGGCAACA GCATCCTTCA CATTACATAT 2126 CAGCATCAAA GGCAGCATTG CAAGGCTTCT TTCATTACCC TTACTTGAAT TACCTTGACA ATAAAATTTC TGAAGCAGAC CTAACTAAGC TTTCCTTTGG AAATCAGATA TGGATCAATG 2246 TGTGAATTGT CCAGAATACC AATATGCCAA CACAGAACAG AACAAATGTA TTCAGAAAGG 2306 TGTCACCTTC CTAAGCTATG AAGACCCCTT GGGGATGGCA CTTGCCTTAA TGGCCTTCTG 2366 CTTCTCTGCA TTCACAGCTG TGGTACTTTG TGTCTTTGTG AAGCACCATG ACACTCCTAT 2426 TGTGAAGGCC AATAACAGAA GCCTCAGCTA CCTATTACTC ATGTCACTCA TGTTCTGTTT 2486 TCTGTGCTCC TTTTTCTTCA TTGGCCTTCC AAACAGAGCC ATCTGTGTCT TACAGCAAAT 2546 CACATTTGGA ATTGTATTCA CTGTGGCTGT TTCCACAGTT CTGGCCAAAA CAGTCACTGT GGTTCTGGCT TTCAAAGTCA CAGACCCAGG GAGAAGATTG AGAAACTTCC TGGTATCAGG 2666 GACACCCAAC TACATTATTC CCATATGTTC CCTACTCCAA TGTGTTCTGT GTGCAATCTG GCTAGCAGTT TCTCCTCCCT TTGTTGATAT TGATGAACAC ACTCTCCATG GCCATATCAT CATTGTGTGC AACAAGGGCT CAGATACTGC ATTCTACTGT ATCCTGGGAT ATTTGGCCTG 2786 CCTGGCACTT GGAAGCTTCT CTCTGGCCTAG AATCTGCCTG ACACATTCAA 2906 TGAAGCCAAA TTCTTGACCT TCAGCATGCT AGTGTTCTGT AGTGTCTGGG TCACCTTCCT CCCTGTCTAC CATAGCACCA AGGGCAAACA CATGGTTGCT GTGGAGATCT TCTCCATCTT 3026 GGCATCCAGT GCAGGGATCC TTGGATGTAT TTTTGTACCC AAGATTTATA TCATTTTAAT GCGACCAGAG AGAAATTCTA CCCAAAAGAT CAGGGAAAAA TCATATTTCT GAACAAATAT 3146 TTAGGAATTC TGTCAAATGT AAAGTTGGTA CATACCCACC AAATATTGGG TTATAGTGCA 3206 TGTGTCTAGT TTTAGAATCA CTCTCACTGG TTGCTCTAGT GATATCAGGA AGTATCATAT 3266 CTACTGAACT TCCCTACAGT GTCCATAAAA TCTTGCACTC ATTCACTTTC TTCATTTTCT 3326 CTCAGAGAAC TAAACTCTCA ATTATTACAA TTTTATTCTT CATTTTGATT TCATGGAGAT GGCCCTCTGG TAACTGCCAA AAAATGTTGA TAAGGCAGTT GAATCCACCA CTTTGTGTAG AAAAATGAGA TCTAGGAAGA CAGGGTTACA CATAAAAACC ATCTACCAAA TCAAATAATC AATGAGAAAC ACAGACTAAC TAAATAATCA GCAAAGATGA AATCAGAACA TATTTTCTGA 3566 TTTCCAGTAA GAGCACACA ATAAGAAAAT ACTTACTTTT TTCATCTGTT CTTCAATCTA CTGGCCAATA GTCTAAGGAG GAAATGTTCC TTTTCTGCTG TCAAATAAAA ATATATTATA 3686 TCC

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 127 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Phe Ile Phe Met Gly Val Phe Phe Leu Leu Asn Ile Thr Leu Leu 10 Met Ala Asn Phe Ile Asn Pro Arg Cys Phe Trp Arg Ile Asn Leu Asp 20 25 Glu Ile Thr Asp Glu Tyr Leu Gly Leu Ser Cys Thr Phe Ile Leu Ala **35** . 40 45 Ala Val Gln Thr Pro Thr Glu Lys Asp Tyr Phe Asn Lys Thr Leu Asn 55 60 Val Leu Lys Thr Thr Lys Asn His Lys Tyr Ala Leu Ala Leu Val Phe 70 Ala Met Asp Glu Ile Asn Arg Asn Pro Asp Leu Leu Pro Asn Met Ser Leu Ile Ile Arg Tyr Thr Leu Gly Leu Cys Asp Gly Lys Thr Val Thr .

PCT/US98/13680

721

781

841

901 961

1081

1141

1201

1261

1321

1381

1441

- 120 -

100 105 Pro Thr Pro Tyr Leu Phe His Lys Lys Lys Thr Lys Pro Tyr Pro 120

- (2) INFORMATION FOR SEQ ID NO:31:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 3896 base pairs
 (B) TYPE: nucleic acid

 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 36...263
 - (D) OTHER INFORMATION:
- /wil SECTIONS DESCRIPTION, SEC ID NO. 33

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:										
ATTTCACAAC TTCTTGATCT TAGACCTTAG CAGAT ATG AAA AAC CTG TGT GTT Met Lys Asn Leu Cys Val 1 5	53									
TTC ACT CTT TCC TTT TTC CTC CTG GAG TTT TCT CTG ATC TTG TGC CAT Phe Thr Leu Ser Phe Phe Leu Leu Glu Phe Ser Leu Ile Leu Cys His 10 15 20	101									
TTG ACT GAA CCC ATT TGC TTT TGG AGG ATA AAT AAT AAT GAA GAT AAT Leu Thr Glu Pro Ile Cys Phe Trp Arg Ile Asn Asn Glu Asp Asn 25 30 35	149									
GAT GGA GAT TTG AGA AGT GAC TGT GGT TTT TTC CTT GCA GCA GTT GAG Asp Gly Asp Leu Arg Ser Asp Cys Gly Phe Phe Leu Ala Ala Val Glu 40 45 50	197									
GGA CCT ACT GAC GAC TCT TAT AAT ATC TCT GAT CTT AGG TTT TCT TTG Gly Pro Thr Asp Asp Ser Tyr Asn Ile Ser Asp Leu Arg Phe Ser Leu 55 60 65 70	245									
GAC CAT TTA ATC CTA AGC TGAGTGACCA TGACCAGTTT CCCTATGTCC ATCAGGTA Asp His Leu Ile Leu Ser 75	301									
GCCACCAAGG ACACACGTTT GTCCCATGCA ATGGTCTCCT TGATGTTTCA TTTTACATGG	361									
ATTTGGATAG GAATGGTCAT CTCAGATGAT GACCAGAGTA TTCAGTTTCT ATCAGACATG	421									
AGAGAAGAA TGCAAAGACA TGGAATCTGT TTAGCTTTTG TTAATATGAT CCCAGAAGAC	481 541									
ATGCAGTTAT ATATGACAAG GGCTACAATA TATGATAAAC AAATTATGGA ATCAACAGCA AAGGTTGTTA TGATTTATGG TGAAATGAAC TCTACCTTAG AAGTTAGCTT TAGAAGGTGG	601									
GAAGATTTAA GTATAAGGAG AATCTGGATC ACAACCTCAC AATGGGACGT TATCACAAAT	661									

AAAAATGATT TCAGCCTTGA TTTCTTCCAA GGGACTGTCA CTTTTGCACA CCATGTAGGT

GAAATTGCTA ACTTTAGGAA TTTCTTGCAA ACAATGAACA GTGAAAAATA CACAGTAAAC

ATTTCTGAGT CTAGACTGGG GTGGAATTAT TTTAATTGTT CCATCTCTAA GAACAGCAAT

AAAAAGGATC ATTTTACATT CAACAACACA TTGGAATGGA CAACACTGCA CAAATATGAC ATGGTCCTAA GTGAGGAAGG CTACAATTTG TATAATGCTG TGTATGCTGT GGCCCACACC

TACCATGAAC TCGTTCTTCA ACAAGTAGAA TCTCAGCAAA TGACAGTACC CAAAGGAACA TTCACTGACT GTCAGCAGGT GTCTTCCATG CTGAAGTCCA GGATATTTAC TAACCCTGTT

GGAGAACTGG TGAACATGAA GCATAGGGAA AATCAGTGTA CAGAGTATGA TATTTTCATC

ATTTGGAATT TTCCACAAGG CCTTGGATTA AAAGTGAAAA TAGGAAGCTA TTTGCCTTGT

TTCCAACAGA GCCAACAACT TCATATATCT GAAGATTTGG AGTGGGCCAC AGGAGGATCA

TCAGTACCCC CCTCCCTGTG TAGTGTAACA TGTACTGCTG GATTCAGGAA AATTCATCAG

AAACAAACAG CAGACTGCTG CTTTGATTGT GATCAGTGCC CAGAAAATGC AGTTTCCAAT

GAAACAGAGA TATGCAATCT GAACATGGAA AGACCATCAT TATTTGCAAC AAAGGCTCAG

TAATTGCCTT CCACTTTGTT CTCGGATACT TGGGTGCCTT GGCTCTGGGG AGCTTTACTG TGGCTTTCTT GGCTAGGAAC CTTCCTGACA GATTCAATGA AGCCAAATTC TTAACCTTCA GCATGCTGGT GTTCTGCAGT GTCTGGATCA CCTTCCTCCC TGTCTACCAC AGCACCCAGG GAACGGTCAT GGTGGTTGTG GAGGTTTTCT CCATCTTGGC TTCTAGTGCA GGCTTGCTAG GGTGTATCTT TCTCCCAAAA TGTTGTGTTT TATTACGTAT ACAAAATTCA AACTTTCTGC ATAAGTACAA ACATGAATTG CATTCTTGAT TCTTTAGTAA TTTAAAAATG CTAATCATAC TCAACTTATC TTTTTGCTTT GTCATAACAA AAGCACCACT AAATCATACA AAAAATTTAA GTAATATACA AATTTAGTAT TTACAATGTA GGGCAGCACA GCACTGCCTA ATGTAATGCC AATTATTGTT TTAGAGGTAA ATGGTCTTAT TCATGTGTAC ATAGATGTAA ACATTGAGAA TAGGGAATCT AACTTGATGA ATGGCTATCA ACACTTTGAC CTCTAGGTAT GTGTGTAAGC CATGTACCTA ATTTAATATG TAATAAGGTG AGCGTAACAT ATGTGAGAGT GCTACCTCTG GGCAGAAAGT TCTGGGAATT ATAAGAAAGA GGACTTCAAA GAGCACAGGC ATGAAGTCAA TAATCAGCAT TATTCCATGT GCTCTCATTG AGTGTCTGCA TCCACGTTCT TGTCTTGACT TCATTCTATT AACTGTGACT AAGGTACATA GGGAAATAGG ACTTTTCTCA CATGGTTCCT TTGACCATGG TGTTTTCTTA CAGCAACAGA CTCTAAGACA TCAGCAAAAT GTTAAATTGC CTTGGTTAGG ATTTGGAATA TCACAGATTA CTGATGCAAT AGAAGGCACT GATTTGAAAG AGAAAATAGA TTGAATACTA GGGGAGTGTG AGCATAGTTA CAGTGTTGCA TATTGTTGAT GGCCATCACA GAGGCCTGAG ATTTGTAATT GCTTCATAAT GTACTATGAA AATATTCAGA 2521 ATATCAGGTA ACATACTAAA AGAAGTACAA TATATGAAAA GGACAATGGG GTTCAGATTA TGCCTGCTCT ATAAGGCTCA TGAACTTCAT ATGAAAACAT ACCATTTCAA TATGAAATGA AGAAGTTTCA TTCAGGGAGA AAAATTGGTA GTGGAAAAAT TTACACACAA GACCTATATC ACAAGGAGAT CAGTGAAATC TTGGAATATA TAAGGCACTC TAGAAGAATG ACTTCAAAAA TGTTAGCAAA ATAGGAACAA CTAAGAATTA TTTGGTTTAA TATTACATAA TCAAAGATGT ACATACAAAC ACATGAACAT TATTATTTCT GGACGTCAGT TGCTGAAGGT CAGTGTCATT TTCTCTCAAA GTATTGTTTG TTGCTCTTAT TTTACTTGTT AATTTACAGT TTATTTTTGA 2941 TGGGATAATT TAATTGTTTT TTTCTTTATA TTTCCTGTCT CAAGAACACC ACTTGTAGCC CATCCATACA CTCCTAAAAT GCAAATGACC TATTATTTCA TTAATGCTTA ATGAATGCAT 3061 GCATGTATTT GTATATACAT ATACATTTTA AAGTATACAT TGTAGATACT ATGTAAAATT GCATGTTTTT ATGTTTTGAT GGCTCATTAT TTGGTAATAC CTGGCCAATA TTTGTTCCCT TCCCTGGCTA TGACAACCTC CTCCATTCCC TGATTTAAAG TTTCCTGTAA ATGGTTGTGT AGGGTAGAAG CTTTGAAAGC TTTCTTCCTT CCACGCTGCC ATGCACAGTG CAGTAATCCT TCTTCAGACC ATATTTTGTG TGTCATATTG GTAAAACTTC ATGGTCTACT TATGCTAGTT CTAGAAGATT TGTGTTCACA GCCAGTTTCC TCATCCTTTG ACTCACAAGA TCTTTTCCAC 3421 CATCTTCTTT ACGTTTCTCT GAGCCTTGGA TGAGGGGAAAA TTTTGTAAGA GGATACATTG AATTGTTTCC TTCAACTACC TACTCTGGAA ATGACTATCA CACTATCACA ACATCTTTAA 3541 AAACAAGATG GAACTCCAAA ATCATTTTCT AAGGAAATAA ATGAAAATCT AAGTGTTCTT TTAATCTGGT TCATTGGAAT TTCCTGCATT TATCTGCCTG GGTGTATGTA ATCCCCCCCC CCCAGCCTGA AACCTGGCTG AACAGGTTTC ACTGTTAGCA CGAAGAGAGA ATCCGGGGTG 3721 GAGCCTTCCA CCCTATCATT CTGCCACTCC CACTGCTACT GCCTGCCGCC CAGCTGTTCC GGAGCTATCA CGTGGTCACC TGAAATTGGA CTCCAAGGAT GATTTGGAGG GAATGGGTGC 3841 CTTCCCCTTC TTCATAAACC AGTGTCTGGG AATAGTAAAA TTGAACTTTG ATCAG

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 76 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

 Met
 Lys
 Asn
 Leu
 Cys
 Val
 Phe
 Thr
 Leu
 Ser
 Phe
 Phe
 Leu
 Leu
 Glu
 Phe
 Phe
 Leu
 Leu
 Cys
 His
 Leu
 Thr
 Glu
 Pro
 Ile
 Cys
 Phe
 Trp
 Arg
 Ile

 Asn
 Ile
 Ile
 Asn
 Ile
 I

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2811 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
 (ix) FEATURE:
- - (A) NAME/KEY: Coding Sequence (B) LOCATION: 962...2605
 - (D) OTHER INFORMATION: GOVN1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GAAACGTCTA CTAATATGCT GTTCTCTTGG CTTTTTATCT CCTTGTTTCT ACAGATGCCA	60
ACTCTCATCT GGACCATTGC AACCCCTTCC TGCCTAACTG AATCAGGATA CCTCGTACAC	120
CAGGATGGAG CTGTGGTCAT TGGTGCATTT TTTCCTGTTT TAAAGTCCTT GCCTATAAGT	180
GAAATAATAG ATTGGAAAAC ATTATCTTTT GACACATACA ATTCTTTATG GATAAATGCA	240
CAAATGTACC AACTTGTTTT GGCCATGATA TTTGCGATCA ATGAGATCAA TGTGAAGTCC	300
CATATTTTAC CAAATACCTC TCTGGGACTT GAGATTTATA ATCTGCCATA TTTTGAACGG	360
AATATTCTGA GGAGTGCACT ATCTTGGCTC ACAGGCTTGA GCAAATTCAT TCCTAATTAC	420
ACCTGCAGAA AGGATAGCAA ATCAGCTGCT GCACTTACTG GAATATCACA GAAAACATCT	480
GAGACCTTTG GGACTTTGTT GGACATTTAC AAATTTCCTC AGCTTAATTT TGGGCCGTGT	540 600
GATCCTGTTC AGATAGGCAG AAACCAGTTT CCATCTGTGT ACCAGGTGGC CCCCAAAGAC	660
ACACCTCTGT TCTGTGGTAT CACCTCTTTG ATGCTTCATT TCAACTGGAC CTGGGTGGGA	720
CTGCTAATCA CAGATGACAA CAGAGGTTCT CAGTTTCTAT CAGAGTTAAG AAAGGAGCTG GACAAGAATA AAATCTGCAT AGCCTTTGTG GAAACAGTAA TATTTTTTGG GGAATCATTG	780
CATTATATGC TAACCCACAA TCAGATGCAG ACTCTAGAGT CATCAGCAAA TGTGATTATA	840
GTTTATGGAC ATTTTGCTTT TCAATTAATT GTAATACAAA GTAAACACAG AAAGTATGAA	900
ATGAAAAAGA TTTGGGTCAT AACCTCAAAA TGGGTTGGCC AAAAAAATTG AACAATATAC	960
C ATG TTA GAA TTG GCC CAT GGC ACT CTG ACT TTC TCA CCC CAT CAT GGG	1009
Met Leu Glu Leu Ala His Gly Thr Leu Thr Phe Ser Pro His His Gly	1005
1 5 10 15	
1 2 2	
GAG ATT TOT GAT TTC ACA AAT TTT ATG CAG GAA GTC ACC CCT ATC AAG	1057
Glu Ile Ser Asp Phe Thr Asn Phe Met Gln Glu Val Thr Pro Ile Lys	
20 25 30	
20 23	
TAC CCA GAA GAC ATT TTT CTT CAC ATC TTG TGG AAC CAG TAT TTC AAT	1105
Tyr Pro Glu Asp Ile Phe Leu His Ile Leu Trp Asn Gln Tyr Phe Asn	
35 40 45	
55	
TGT CCA CTT TTG CAT TCT GAG TGT AAA ATC TTT GAA AAC TGT ATA CCC	1153
Cys Pro Leu Leu His Ser Glu Cys Lys Ile Phe Glu Asn Cys Ile Pro	
50 55 60	
30 30	
AAT GCC TCT TTG GAA TTG TTG CCA GGG GGT GTT TTT GAG CTG GTC ATG	1201
Asn Ala Ser Leu Glu Leu Leu Pro Gly Gly Val Phe Glu Leu Val Met	
65 70 75 80	
ACT GAA GAG AGT TAC AAT GTG TAC AAT GCT GTG TAT GCA GTG GCC CAC	1249
Thr Glu Glu Ser Tyr Asn Val Tyr Asn Ala Val Tyr Ala Val Ala His	
85 90 95	
35	
AGT CTC CAT GAG AAG GCT CTC CAT CAA GTA GAA ATT CAA CCA CAG GAT	1297
Ser Leu His Glu Lys Ala Leu His Gln Val Glu Ile Gln Pro Gln Asp	
100 105 110	
100 103 110	
AAT AAA GAT AGG ACT ATA TTA TTT CCT TGG CAG CTT CAC CCT TTT CTG	1345
Asn Lys Asp Arg Thr Ile Leu Phe Pro Trp Gln Leu His Pro Phe Leu	
115 120 125	
120 120	

		_	CAG Gln						_							1393
			AAG Lys													1441
			GGT Gly													1489
			AAG Lys 180									-				1537
			GGA Gly													1585
			GGA Gly													1633
			TGC Cys													1681
			CAG Gln													1729
			CAC His 260									-				1777
			GGG Gly													1825
			CTT Leu													1873
			GCC Ala													1921
			TGT Cys						_							1969
			TGT Cys 340													2017
			TCC Ser												GCA Ala	2065
			ACT Thr												TTA Leu	2113
AGA	GCC	CCT	CAG	TTC	ATC	ATT	CCA	CTT	TGT	GCC	CTG	ATG	CAA	ATC	CTT .	2161

- 124 -

Arg 385	Ala	Pro	Gln	Phe	Ile 390	Ile	Pro	Leu	Cys	Ala 395	Leu	Met	Gln	Ile	Leu 400	
														ATG Met 415		2209
														GGC Gly	TCA Ser	2257
														GCC Ala		2305
											-			ACA Thr		2353
														AGT Ser		2401
														GTC Val 495		2449
														ATT Ile		2497
								Tyr						CCA Pro		2545
															AAA Lys	2593
	TCT Ser			TAG	CAGTO	CAA (JACA)	AACA	rt G	3CCT2	AGCA(C AAJ	AATG:	rctg	ATTGT	2650
GAC	AGAC	CGG :		ATTG	CT TO	CAAAT	TAT	TAJ	TAAA	ATGT	GAC				ACATGA BACCAA	2710 2770 2811

(2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 548 amino acids
 (B) TYPE: amino acid

 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Leu Glu Leu Ala His Gly Thr Leu Thr Phe Ser Pro His His Gly 10 Glu Ile Ser Asp Phe Thr Asn Phe Met Gln Glu Val Thr Pro Ile Lys 20 25 Tyr Pro Glu Asp Ile Phe Leu His Ile Leu Trp Asn Gln Tyr Phe Asn .

Cys Pro Leu Leu His Ser Glu Cys Lys Ile Phe Glu Asn Cys Ile Pro Asn Ala Ser Leu Glu Leu Leu Pro Gly Gly Val Phe Glu Leu Val Met Thr Glu Glu Ser Tyr Asn Val Tyr Asn Ala Val Tyr Ala Val Ala His Ser Leu His Glu Lys Ala Leu His Gln Val Glu Ile Gln Pro Gln Asp Asn Lys Asp Arg Thr Ile Leu Phe Pro Trp Gln Leu His Pro Phe Leu Lys Asn Ile Gln Leu Ile Asn Ser Val Gly Asp Arg Val Ile Leu Asp Trp Lys Lys Lys Thr Asp Thr Glu Tyr Asp Ile Ser Asn Ile Trp Asn Phe Pro Thr Gly Leu Ser Leu Leu Val Lys Val Gly Thr Phe Ala Pro Ser Ala Pro Lys Gly Glu Gln Leu Ser Ile Ser Glu His Thr Ile Asn Trp Pro Ile Gly Phe Thr Glu Ile Pro Lys Ser Val Cys Ser Glu Ser Cys Ser Pro Gly His Arg Lys Val Ile Leu Glu Ser Lys Pro Ala Cys Cys Phe Asp Cys Thr Pro Cys Pro Asp Lys Glu Ile Ser Asn Glu Thr Asp Val Gly Gln Cys Val Lys Cys Pro Glu Ser His Tyr Ala Asn Thr Glu Lys Ser His Cys Leu Lys Lys Thr Met Thr Phe Leu Asp Tyr Asn Asp Ser Leu Gly Thr Gly Leu Thr Leu Met Ser Leu Gly Phe Phe Val Val Thr Gly Leu Val Ile Gly Val Phe Ile Ile His Arg Asn Thr Pro Ile Val Lys Ala Asn Asn Arg Ser Leu Ser Tyr Ile Leu Leu Ile Thr Leu Thr Leu Cys Phe Leu Cys Pro Leu Leu Phe Ile Gly Leu Pro Asn Thr Ala Thr Cys Ile Leu Gln Gln Asn Leu Phe Gly Leu Leu Phe Thr Val Ala Leu Ser Thr Val Leu Ala Lys Thr Ile Thr Val Val Met Ala Phe Lys Ile Thr Ala Pro Gly Arg Lys Thr Arg Trp Leu Leu Ile Leu Arg Ala Pro Gln Phe Ile Ile Pro Leu Cys Ala Leu Met Gln Ile Leu Phe Ser Gly Ile Trp Leu Gly Thr Ser Pro Pro Phe Val Asp Met Asp Ala His Ser Glu His Gly His Ile Ile Leu Cys Asn Lys Gly Ser Ala Ile Gly Phe Tyr Cys Thr Leu Ala Tyr Leu Gly Val Met Ala Phe Gly Ser Tyr Leu Leu Ala Phe Met Ser Arg Asn Leu Pro Asp Thr Phe Asn Glu Ser Lys Ala Leu Ala Phe Ser Met Leu Met Phe Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Thr Gly Lys Val Arg Val Ala Met Glu Met Phe Ser Ile Leu Ala Ser Ser Ala Ser Ile Leu Thr Leu Ile Phe Val Pro Lys Cys Tyr Ile Val Leu Phe Arg Pro Glu Arg Asn Ile Leu Pro Leu Asn Arg Glu Lys Arg Gln His Arg Ser Lys Asn Ser Glu Thr

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3584 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:

(A) NAME/KEY: Coding Sequence(B) LOCATION: 273...2576(D) OTHER INFORMATION: GOVN2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

						~										
															TCCTT	60
															CAAAT	120
															CAGTT	180
															TAAAA	240
ACA	CAA	TA T	rgcc1	TGG	CA TT	ragec		' CA								293
										Glu	Glu	Ile		Arg	Asn	
									1				5			
ССТ	GAT	CTT	TTA	CCA	AAT	ATG	TCT	TTG	GTT	ATA	AAA	CAT	ACT	TTG	AGC	341
			Leu													
		10					15				-1-	20				
			GGA													389
Tyr	Cys	qsA	Gly	Asn	Thr	Ala	Asp	His	Ile	Phe	Lys	Glu	Lys	Phe	Tyr	
	25					30					35					
מממ	ССТ	מידיים	CCT	ייעמ	тат	GTC	тст	ידעע	aan	GAG	ΔСТ	λ ጥር	ጥርጥ	דר ם	thatate	437
			Pro													
40					45	*~	Cys	*1011		50		ricc	Cys		55	
40					13					30					JJ	
ATG	CTT	ATA	GGG	CTG	AAT	TGG	GTA	TTG	TCT	CTA	ACA	CTT	TTT	AAA	GAC	485
Met	Leu	Ile	Gly	Leu	Asn	Trp	Val	Leu	Ser	Leu	Thr	Leu	Phe	Lys	Asp	
			•	60		-			65					70	-	
TTG	GAC	ATC	TTC	TCA	TTT	CCA	CGT	TTC	CTT	CAA	ATT	TCC	TAT	GGA	CCT	533
Leu	Asp	Ile	Phe	Ser	Phe	Pro	Arg	Phe	Leu	Gln	Ile	Ser	Tyr	Gly	Pro	
			75					80					85			
mma	C N TT	maa	3.00	mma	3 C C	CAM	220	C 3 3	~ n n	mmm	CC3	mam	omo.	m a m	CAC	581
			ATC													201
Pne	HIS		Ile	Pne	ser	Авр		GIU	GIN	Pne	PIO	-	ren	Tyr	GIN	
		90					95					100			•	
ATG	ACC	CCA	AAG	GAC	ACA	TCA	CTA	GCA	TTG	GCA	ATT	GTC	TCC	TTC	TTA	629
			Lys													
	105		-4-			110					115					
CTT	TAC	TTC	AAT	TGG	AAC	TGG	GTT	GGG	CTT	GTC	ATC	TCT	GAT	AAT	GAT	677
Leu	Tyr	Phe	Asn	Trp	Asn	Trp	Val	Gly	Leu	Val	Ile	Ser	Asp	Asn	Asp	
120					125					130					135	
~~~	~~~		<i>~</i> >>				~~~				~~~					
			CAA								•					725
GIU	GIA	Asn	Gln		Leu	ser	GIU	ьeu	•	гÀв	GIU	Thr	GIn		ràs	
				140					145					150		
GAA	ATT	TGC	TTT	GCC	TTT	GTT	AAC	ATG	ATG	TCA	ATC	CAT	GAG	CAT	TCA	773
			Phe													
		-,-	155		2 2			160					165			
															•	

					GAA Glu											821
•	-3-	170	_,				175	-1-				180				
					ATT Ile											869
					GTA Val 205											917
					TTC Phe											965
					CTG Leu											1013
					TTC Phe											1061
					CCA Pro											1109
					ATA Ile 285											1157
					CAG Gln											1205
					GCT Ala											1253
					GTT Val											1301
					TTG Leu											1349
TTT Phe 360	ACT Thr	AAT Asn	TCT Ser	CAT His	GGA Gly 365	GAG Glu	AGA Arg	GTG Val	ATT Ile	ATG Met 370	AAA Lys	CAG Gln	AGA Arg	GTG Val	AGA Arg 375	1397
					GAC Asp											1445
					AAG Lys											1493
					TTA Leu											1541
AGT	AGA	AAG	ATG	CCG	TCC	TCT	GTG	TGC	AGT	GCA	GAT	TGT	AGT	CCT	GGA .	1589

Ser	Arg 425	Lys	Met	Pro	Ser	Ser 430	Val	Cys	Ser	Ala	Asp 435	Cys	Ser	Pro	Gly	
			TCC Ser													1637
			CCT Pro													1685
			TGT Cys 475													1733
			AAA Lys													1781
			GCC Ala													1829
			GTC Val													1877
			ATC Ile													1925
			TCC Ser 555									-				1973
			CAA Gln													2021
	_		GCC Ala													2069
			AGA Arg													2117
			CCT Pro													2165
			GTT Val 635													2213
	Gly		ATC Ile													2261
			CTA Leu													2309
			TTG Leu												AAG Lys .	2357

- 129 -

680	685	690	695
TTC TTG ACC TTC AGC Phe Leu Thr Phe Ser 700			
CTC CCT GTG TAC CAT Leu Pro Val Tyr His 715			a Val Glu
ATC TTC TCT ATC TTG Ile Phe Ser Ile Leu 730			
GCA CCC AAA ATC TAC Ala Pro Lys Ile Tyr 745			
CAA AAG TTC AGG GAG Gln Lys Phe Arg Glu 760			AAT TTAGTTG 2603
AATATTAAGT TGGTATAT	AC CCACCAAATA TT	TGGTTATT GTGCATGTAT	AGAGTTTTAG 2663
AATCAGTCTT ACTGATTC	CT CTATTGCTGT CT	AGAGGTAT CTTATCTACC	AGTCTTGCAT 2723
ACATTGTCCA TAAAATCT	IG TACTCATTCA CT	TCTTTAGT TTCCTCTGAG	AAAACTAAAT 2783
TTCTCAAATT ATTACTAA	AA TGTAATTCAA CA	TTATGCTT TCATGGATAT	TTCCCCCTGG 2843
TTACATCAGA TAAATTTG	AT AAGACAGCTG AT	TTTGTTAC CTTATATAGA	AGGTATATGA 2903
ATGTCCTGCC TTACAGGA	CA GAGAGGAATT AC	ACTTAGAA ACCGTCTATC	AAGTCAAACA 2963
TTCAATCATA CTGAAAAA	ra aactaaagga tc	AACAGAGA TAAAAAGCAG	AATACATTTT 3023
CTGTTTTCTA GTCGGAGC	AT ATACATGACA GA	ATTCTGTT TTTATTTACA	GTTGCTCTTC 3083
AAGGTTTTGG TCAATAGT	CT AAGATGCAAA TG	TTTTCTTT TTTTCTGATC	тсааааааа 3143
TATTATAGCC AACAATTG	aa agaagccagt ga	CCACTGTG TTTAAATTAG	GAACTAGTTT 3203
GAGGATCCTG AGAAGGAG	GG TGACTCATTG GA	AGACCAGC AGTCTTATCT	AACCTGAATA 3263
ACAAAGAATT TTCAGACA	CT GAGCCTCTAA CC	GGGCAGCA TACACCAGTT	GATATGAAGC 3323
CCCCAACATA TATGCAACA	AT AGGATGTCCT GG	TCTGGCCT TGGTGAGAGA	
AACCCCCAAG AGACATGA			
ACTACTTCTT GATGCTGG			
GAAAGGGATA ATGAGTTC	AC AGTAAAAAAA AT	GTTAAAGA ATAAAAATCT	
TAAAAAAA AAAAAAAA	AA A		3584

# (2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 768 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Glu Glu Ile Asn Arg Asn Pro Asp Leu Leu Pro Asn Met Ser Leu 10 Val Ile Lys His Thr Leu Ser Tyr Cys Asp Gly Asn Thr Ala Asp His 25 20 30 Ile Phe Lys Glu Lys Phe Tyr Lys Pro Leu Pro Asn Tyr Val Cys Asn 35 40 45 .* Glu Glu Thr Met Cys Ser Phe Met Leu Ile Gly Leu Asn Trp Val Leu 50 55 60 Ser Leu Thr Leu Phe Lys Asp Leu Asp Ile Phe Ser Phe Pro Arg Phe 70 75 Leu Gln Ile Ser Tyr Gly Pro Phe His Ser Ile Phe Ser Asp Asn Glu 85 90

Gln Phe Pro Tyr Leu Tyr Gln Met Thr Pro Lys Asp Thr Ser Leu Ala Leu Ala Ile Val Ser Phe Leu Leu Tyr Phe Asn Trp Asn Trp Val Gly Leu Val Ile Ser Asp Asn Asp Glu Gly Asn Gln Phe Leu Ser Glu Leu Lys Lys Glu Thr Gln Asn Lys Glu Ile Cys Phe Ala Phe Val Asn Met Met Ser Ile His Glu His Ser Ser Tyr Gln Lys Thr Glu Met Tyr Tyr Asn Gln Ile Val Met Ser Ser Thr Asn Ile Ile Ile Tyr Gly Lys Thr Asn Ser Ile Ile Glu Leu Ser Phe Arg Met Trp Val Ser Pro Val Ile Gln Arg Ile Trp Val Thr Asn Ser Glu Leu Asp Phe Pro Thr Ser Met Arg Asp Phe Thr His Gly Thr Phe Tyr Gly Thr Leu Thr Phe Leu His His His Gly Glu Ile Ser Gly Phe Thr Asn Phe Phe Glu Thr Trp Asp His Leu Arg Ser Arg Asp Leu Asn Leu Leu Ile Pro Glu Trp Lys Tyr Phe Ser Tyr Asp Ala Ser Gly Ser Asn Cys Lys Ile Leu Arg Asn Tyr Ser Ser Asn Ala Ser Leu Glu Trp Ile Thr Glu Gln Lys Phe His Met Ala Phe Asn Asp Tyr Ser His Ser Ile Tyr Asn Ala Val Tyr Ala Met Ala His Ala Leu His Glu Thr Asn Leu Gln Glu Val Asp Asn Lys Glu Ile Arg Asn Gly Lys Gly Ala Ser Thr His Cys Leu Lys Val Asn Ser Phe Leu Arg Lys Thr His Phe Thr Asn Ser His Gly Glu Arg Val Ile Met Lys Gln Arg Val Arg Val Gln Glu Asp Tyr Asp Ile Val His Ile Gln Asn Phe Ser Gln His Leu Arg Ile Lys Met Lys Ile Gly Lys Phe Ser Pro Tyr Phe Thr His Gly Gly Pro Phe His Leu Tyr Glu Asp Met Ile Gln Leu Ala Thr Gly Ser Arg Lys Met Pro Ser Ser Val Cys Ser Ala Asp Cys Ser Pro Gly Phe Arg Lys Ser Trp Lys Glu Gly Met Ala Pro Cys Cys Phe Ile Cys Ser Leu Cys Pro Glu Asn Glu Ile Ser Asn Glu Thr Asn Met Asp Gln Cys Val Asn Cys Pro Glu Tyr Gln Tyr Ala Asn Thr Glu Lys Asn Lys Cys Ile Gln Lys Asp Val Ile Phe Leu Ser Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Leu Ile Ala Phe Cys Leu Ser Ala Phe Thr Ala Val Val Leu Trp Val Phe Val Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Ile Leu Ile Met Ser Leu Met Phe Cys Phe Leu Cys Ser Phe Phe Phe Ile Gly His Pro Asn Arg Gly Thr Cys Ile Leu Gln Gln Ile Thr Phe Gly Ile Val Phe Thr Val Ala Val Ser Thr Val Leu Ala Lys Thr Ile Thr Val Ile Leu Ala Phe Lys Leu Arg Asp Pro Gly Arg Ser Leu Arg Asn Phe Leu Val Ser Gly Ala Pro Asn Tyr Ile Ile Pro Ile Cys Ser Leu Leu .

615 620 Gin Cys Ile Leu Cys Ala Ile Trp Leu Ala Val Ser Pro Pro Phe Val 630 635 Asp Ile Asp Glu His Ser Glu His Gly His Ile Met Ile Val Cys Asn 645 650 655 Lys Gly Ser Ile Met Ala Phe Tyr Cys Val Leu Gly Tyr Leu Ala Cys 665 660 670 Leu Ala Leu Gly Ser Phe Thr Thr Ala Phe Leu Ala Lys Asn Leu Pro 675 680 685 Asp Thr Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe 695 690 700 Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Arg Gly 705 710 715 Arg Val Met Val Ala Val Glu Ile Phe Ser Ile Leu Ala Ser Ser Ala 725 730 Gly Met Phe Gly Cys Ile Phe Ala Pro Lys Ile Tyr Ile Ile Leu Met 740 745 Lys Pro Glu Arg Asn Ser Ile Gln Lys Phe Arg Glu Lys Ser Tyr Phe 755 760

### (2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3578 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence(B) LOCATION: 1181...3181(D) OTHER INFORMATION: GOVN3

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CTATCTTGAA GAGTGCTT	TT CTGTGTAACT	TGCTTTGCTG	CACGTTTACA	AATTATTTTT	60
TCTTGGTGAA ATTACTAA	GA TGTTCTCTTT	TCTGTTTGCA	ATTCTTGTCC	TGAAGCTTTC	120
TTTTCCTTTG TGCAGTCC	AA TTGACAACCG	TTGTTTTTGG	AGATTAAAAA	CCAAGACATT	180
TTGGGAAGGA GACAAAGA	AC TTGATTGCTT	TTTTTTTATT	TATACAAGGT	TTGGTCATGT	240
AAAGAATGAA CAGTTCAG	TG GGAATCTAGA	CAAGCGGTTG	ACATCTAAGA	CTATCCACTT	300
GATTTTGACT CTTTATTT	TG CCCTTGAAGA	AATAAACAGG	AACCCCCATA	TTCTACCTAA	360
CATTTCACTG CTAGTTAA	AA TTGAATGTGG	GCTGCTAGAT	GATTGGACAA	TAAACAGTTT	420
ATCTTCTAAA AGAGAAAA	AT ATCTTCCTAA	CTACTACTGT	ATAAATCAGA	GAAGATATTT	480
AATTGTACTT ACAGGACC	AA TGTGGTTAGC	ATCTGTCATA	GTTGGGCCAC	TCCTATACAT	540
AACTAAGAGG CCAGAGAT	GG ATCAACTCAA	CTCTTCTGGC	TCAAATTCTT	CCCTAAAGTC	600
ACTAATTGGA TATGGCTT	TA CTCAGCTTCT	CATTGATTTG	CTTTGCTTGA	ACAATCACTG	660
CCCATTTGTT TTAGTCTT	CT GTCTCCTTTA	TATTCTGGCT	ACAACTGCCT	CTACTGATGC	720
ACATTGAACT GCATGAAC	TC ACAAATTAAC	TCAACACCAT	TGCACTGCAT	TCTTTGCACT	780
GAGTCTCAAA AGTCTGGT	TT AACTCTTCTG	CATTGAACTC	AACTGACTAA	TTAGAACTCA	840
GAAATCTGCA TCCCTCTG	TC TCCTGAGTAC	TTTGATTAAA	GGTGTGTACT	ATCACACCTG	900
CACCTAAACT TTTCTATA	CT AAAAATTTGC	TTTATACTAG	GCTGACCTTG	AACTAAGTGA	960
TCTGCTTGCC TCTGTCTC	CT GCCTTCCAAG	GAATGCCTAT	TTCCCAGCAG	GATATTTTTT	1020
GCCTACAAGT CTTCAGAT	GT GATCCATTAA	GTATAGTCAT	GTTGCTGGAT	TAAAATTCCT	1080
CTACAGATTT AATTTTCT	GA TCCTGAGGCT	AGTGAAACTT	TACTATGGGC	CATTTCACCC	1140
TCTCTTGAGC AACCAAGA	AC TGTATCCATA	TCTTTACCAA	ATG GCT CO	CT AAG GAC	1195
			Met Ala Pi	ro Lys Asp	
			1 .	5	

ACA TCT CTG GCA CTG GCC ATG GTT TCT TTG TTT GTC CAT TTC AGC TGG

Thr Ser Leu Ala Leu Ala Met Val Ser Leu Phe Val His Phe Ser Trp

10 15 20

					GTT Val											1291
					AGA Arg											1339
					GTT Val											1387
					CAG Gln 75											1435
					GAC Asp											1483
					CAA Gln											1531
					GGA Gly											1579
					CAC His											1627
ATC Ile 150	CAG Gln	ACA Thr	GCA Ala	TAC Tyr	CCT Pro 155	TCA Ser	AAC Asn	TAC Tyr	AGT Ser	GAT Asp 160	GAC Asp	TTT Phe	TCT Ser	CTT Leu	GGT Gly 165	1675
					TAT Tyr											1723
					TGT Cys											1771
					ATG Met											1819
					GTG Val											1867
CAA Gln 230	GCA Ala	GAT Asp	ACA Thr	TGG Trp	CAA Gln 235	ATA Ile	GAT Asp	GAT Asp	GGA Gly	AAA Lys 240	GAA Glu	CCA Pro	GAA Glu	TTT Phe	GAC Asp 245	1915
TCT Ser	TGG Trp	CAG Gln	ATG Met	CTC Leu 250	TCT Ser	TTC Phe	CTG Leu	AGA Arg	AAT Asn 255	ATC Ile	CAA Gln	TTT Phe	ATA Ile	AAC Asn 260	CCT Pro	1963
					AAC Asn											2011
TAT	GAG	ATT	CAC	CAG	ACT	TTG	ACT	TTT	TTG	CCA	AAT	CCT	GTA	TTT	AAG .	2059

Ty	Glu	Ile 280	His	Gln	Thr	Leu	Thr 285	Phe	Leu	Pro	Asn	Pro 290	Val	Phe	Lys	
Let	AAA Lys 295	ATA Ile	GGA Gly	ACA Thr	TTT Phe	TCC Ser 300	CAA Gln	AAC Asn	TTA Leu	TCA Ser	CAT His 305	GGT Gly	CGA Arg	CAA Gln	TTA Leu	2107
	T ATG Met															2155
Pro	ACC Thr	TCA Ser	GTT Val	TGC Cys 330	AGT Ser	ATT Ile	CCT Pro	TGT Cys	AGT Ser 335	CCA Pro	GGA Gly	TTC Phe	AGA Arg	AAA Lys 340	TCC Ser	2203
CC:	CAG Gln	CTG Leu	GGA Gly 345	AAG Lys	CCT Pro	GTT Val	TGC Cys	TGT Cys 350	TTT Phe	GAT Asp	TGT Cys	ACA Thr	CCC Pro 355	TGC Cys	CCA Pro	2251
GA)	TAA / Ran	GAA Glu 360	ATT Ile	TCC Ser	AAC Asn	ATG Met	ACA Thr 365	AAC Asn	ATG Met	AAT Asn	CAA Gln	TGT Cys 370	ATC Ile	AAG Lys	TGT Cys	2299
CT	AAT Asn 375	GAT Asp	CAG Gln	TAT Tyr	GCC Ala	AAT Asn 380	CCT Pro	GGA Gly	GGA Gly	ACT Thr	CGC Arg 385	TGC Cys	CTC Leu	AAA Lys	AAA Lys	2347
	ATT Ile															2395
	TTG Leu															2443
TT?	TTG Leu	AAG Lys	CAC His 425	CAA Gln	GAA Glu	ACA Thr	CCC Pro	ACT Thr 430	GTC Val	AAG Lys	GCC Ala	AAT Asn	AAT Asn 435	AGA Arg	ACT Thr	2491
	AGC Ser															2539
	CTC Leu 455															2587
	ACA Thr															2635
AAI Lys	ACA Thr	ATT Ile	ATT Ile	GTA Val 490	ATA Ile	TTG Leu	GCC Ala	TTC Phe	AAG Lys 495	GTT Val	ACT Thr	AAT Asn	ACA Thr	AGT Ser 500	AGA Arg	2683
AAI Lys	ATG Met	AGG Arg	TGG Trp 505	CTG Leu	CTG Leu	GTA Val	TCA Ser	GGG Gly 510	GCA Ala	CCT Pro	AAA Lys	TTC Phe	ATC Ile 515	ATT Ile	CCA Pro	2731
ATT Ile	TGC Cys	ACA Thr 520	ATG Met	ATT Ile	CAA Gln	CTG Leu	ATT Ile 525	CTC Leu	TGT Cys	GGA Gly	ATT Ile	TGG Trp 530	CTG Leu	GGT Gly	ACT Thr	2779
TC7 Se1	CCT Pro	CCA Pro	TTT Phe	GTT Val	GAT Asp	GCT Ala	GAT Asp	GGA Gly	CAT His	GTT Val	GAA Glu	AAA Lys	GGC Gly	CAC His	ATT Ile.	2827

- 134 -

	535					540					545					
TTG Leu 550																2875
GGA Gly																2923
GCC Ala	AGA Arg	AAT Asn	CTG Leu 585	CCC Pro	GAC Asp	ACA Thr	TTC Phe	AAT Asn 590	GAA Glu	GCC Ala	AAG Lys	TTC Phe	CTA Leu 595	ACA Thr	TTC Phe	2971
AGT Ser																3019
CAT . His																3067
TTG Leu 630																3115
TTC . Phe																3163
AAT . Asn						TAAJ	AACA:	TTC 2	ATTAI	AATT:	TT TO	CTGA	CACA	C TTO	<b>ECTA</b> GA	3219
CATG TTAA TATT	GAAT ATCT	TTT ( TTG (	TTC:	CAA: CAT! ATGC:	TA AI AA AI TA TI	AGAAI CAAI TACT	AGGAI ACTG: IGAAC	A GCI F ATC	ACTA: SATC! IGTA!	rgta Agtc Aaga	TTAC ATT	GAAT GAAT	TTA A	AAAAC CTGTT	CCAAA CACGTC CTGCTG CGAGTT CTTGTG	3279 3339 3399 3459 3519
CTCT.	'ATA	ATA A	ATA	TTA:	rg ac	LATAE	AATG	AA.	AAAA	AAAA	AAA	<b>LAAA</b>	AAA 2	LAAAA	AAAA	3578

#### (2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 667 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Ala Pro Lys Asp Thr Ser Leu Ala Leu Ala Met Val Ser Leu Phe 10 Val His Phe Ser Trp Asn Trp Val Gly Ala Val Val Ser Asp Asp 25 Pro Gly Tyr Glu Phe Ile Leu Glu Leu Arg Arg Glu Met Gln Arg Asn 40 45 Asn Phe Cys Leu Ala Phe Val Ser Ile Ile Val Ser Asp Asn Leu 60 Phe Leu Lys Arg Tyr Asn Ile Tyr Tyr Asn Gln Ile Lys Met Ser Ser 70 75 Ala Lys Val Val Ile Ile Tyr Gly Asp Lys Asp Ser Pro Leu Gln Val .

				85					90					95	
Asn	Phe	Arg	Leu 100	Trp	Asn	Leu	Phe	Asp 105	Ile	Gln	Arg	Ile	Trp	Val	Thr
Thr	Ser	Gln 115	Trp	Asp	Met	Ile	Ile 120	Asn	Asn	Gly	Lys	Phe 125		Leu	Asn
	130		Gly			135					140				
145			Thr		150					155					160
			Leu	165					170					175	
			Glu 180					185				_	190		
	_	195	Leu	-			200					205		_	
	210		Leu			215					220	_			
225	MEC	Dea	Leu	шув	230	AIG	Asp	TIII	тър	235	TTE	Asp	Asp	GIY	240
			Phe	245					250					255	
			Asn 260					265					270		
		275	Thr				280					285			
Asn	Pro 290	Val	Phe	Lys	Leu	Lys 295	Ile	Gly	Thr	Phe	Ser 300	Gln	Asn	Leu	Ser
His 305		Arg	Gln	Leu	Tyr 310		Leu	Lys	Glu	Met 315		Glu	Trp	Asn	Thr 320
			Gln	325					330					335	
			Lys 340					345					350		
		355	Сув				360					365			
	370		Lys -			375					380				
385	Cys	Leu	Lys	ьуs	390	TIE	vaı	Pne	Leu	395	Tyr	GIu	Asp	Pro	Leu 400
	•		Leu	405					410					415	
			Ser 420					425				_	430		
		435	Arg				440					445			
	450		Сув			455					460				
465	TTE	Met	Gln	GIN	470	Thr	Pue	ATA	vaı	Val 475	Pne	Tnr	Val	Ala	A1a 480
	Thr	Val	Leu	Ala 485		Thr	Ile	Ile	Val 490		Leu	Ala	Phe	Lys 495	
Thr	Asn	Thr	Ser 500	Arg	Lys	Met	Arg	Trp 505	Leu	Leu	Val	Ser	Gly 510	Ala	Pro
		515	Ile				520					525		_	_
	530		Gly			535					540				
545			His		550					555					560
			Val	565					570					575	
			Phe 580					585					590		
Lys	Phe	Leu 595	Thr	Phe	Ser	Met	Leu 600	Val	Phe	Cys	Ser	Val 605	Trp	Val	Thr

WO 99/00422 PCT/US98/13680 - 136 -

Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys Ser Met Val Ala Val 615 620 610 Glu Val Phe Cys Ile Leu Ala Ser Ser Ala Gly Leu Leu Phe Cys Ile 630 635 625 Phe Ala Pro Lys Cys Phe Ile Ile Leu Leu Arg Pro Glu Lys Lys Ser 645 650 655 Phe Gln Lys Phe Gln Asn Ile His Ser Lys Ile 660

## (2) INFORMATION FOR SEQ ID NO:39:

### (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4467 base pairs (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence (B) LOCATION: 126...2723 (D) OTHER INFORMATION: GOVN4

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CCAC	TGT! CA AT Me	AGA A	AGATO	GGGZ G C	AT AZ	ATTGO SA GO	CTACC CA GO	TGT	TTG(	TGA T AT	TCTC TG CT	TGCA	AGC I	ATTA	CTTGG AACTAC TT TTA Le Leu 15	60 120 170
					AAC Asn											218
					AGT Ser											266
					ATG Met											314
					AGT Ser										GAA Glu	362
					CTC Leu 85											410
					TTG Leu											458
					TTG Leu											506
					GAA Glu											554

			GGA Gly													602
			ATA Ile													650
			GGA Gly													698
			TAT Tyr 195													746
			TTC Phe													794
			AAT Asn												AGA Arg	842
			AAA Lys									_				890
			AAT Asn													938
			TCA Ser 275													986
			GCT Ala													1034
			GTC Val												AAA Lys	1082
			TTT Phe													1130
			ATT Ile													1178
			TCA Ser 355													1226
			ATC Ile													1274
			TCA Ser													1322
ATT	ATT	GAA	GGG	AGT	TAT	GAA	ATA	TAC	AAT	GCT	GTG	TAT	GCT	TTT	GCC	1370

Ile 400	Ile	Glu	Gly	Ser	Tyr 405	Glu	Ile	Tyr	Asn	Ala 410	Val	Tyr	Ala	Phe	Ala 415	
				GAG Glu 420												1418
				GAA Glu												1466
				CAA Gln												1514
				AAA Lys												1562
				GGA Gly												1610
				AAA Lys 500												1658
				GGA Gly												1706
				GGA Gly												1754
				TGC Cys												1802
				TTG Leu												1850
				CAC His 580												1898
				GGG Gly												1946
				GTG Val												1994
				GCC Ala												2042
				TGT Cys												2090
				TGC Cys											TTC Phe .	2138

- 139 -

				_
	660	665	670	
	Ser Thr Val Leu	GCC AAA ACA ACC ACT Ala Lys Thr Thr Thr 680		ļ
		AGA ATG ATG AAG TAC Arg Met Met Lys Tyr 700		:
		CCC ATT TGT ACT CTC Pro Ile Cys Thr Leu 715		
		GCT TCT CCT CCT TCT Ala Ser Pro Pro Ser 730		ŧ
		ATC ATC ATT GCT TGC Ile Ile Ile Ala Cys 745		í
		CTG GGA TAT CTG GCC Leu Gly Tyr Leu Ala 760		ï
		CTT TCC AGA AAC CTG Leu Ser Arg Asn Leu 780		Ė
		TTC AGC ATG CTG GTG Phe Ser Met Leu Val 795		:
		TAC CAT GGC ACC AAA Tyr His Gly Thr Lys 810		,
		ACC TTG GCT TCT AGT Thr Leu Ala Ser Ser 825		š
	Phe Ala Pro Lys	TGC TAC ACA ATA CTG Cys Tyr Thr Ile Leu 840		\$
		AGG GAG AAG TCA TCT Arg Glu Lys Ser Ser 860	Ser His Thr	Ŀ
CAC ATT TTA TAA His Ile Leu 865	AGTCTGA CTGACACAG	G CATTGTTGGT TCATAA	TCAC CAAATATTC 2772	2
TAGCAAGATC ATGT ATCAATCCTA CTCT TTCTTCTAGG AACA AAAGGGGTTG AAGT TACTCAATCC CACC TGGTTTCTTA TTGT ACACACACACAC ACAA	CTACTG AGGACTACCT TTTAGA GAAAGAGATA GAGAAG AGAAAGAATT CACAAC AATATAAATA AACTAC CATTAACAAC CTCCAA ATTTGCCTGA ACACAC ACACAAATA	ACTGTCACTG TTCCCTT TATCTCCTAT AATCTTC ATAGAATTTT AAACATT ATTTTTCAA CAGGTTG AAGCCCTGCT CTTGTAT CACATGTAAC AAATGTT ACTTATTTAT GCACATA AAATTCCATA AAATTTT	CAA CATTTTCTAC 289 TTC AGAATTAGAG 295 ATA GAATATCAGG 301 AGG AACTTATGAA 307 AAA AAGGATCAGA 313 ATG AGACACACAC 319 AAA AATATAGAAT 325	52 52 72 72 32 92
GGAAAATATG GGAC	ATAGGT AGAGATGACT	CTTCAATGTT CATAATT GGGTTTATGT TAAGTCA CAGTTGTGAA ATTTTCA	TTT TAAATAAGAA 337	72

TTGTTGAAAT	AATCTCCATC	TGTGGAATTT	ATAGGGTTTT	GTGACAAAGA	TCAGTTCTGA	3492
TATCAGAGAG	TAAACTGAAG	CAGGCAACCA	TTAGTTGTCA	GCACTGACAG	CAGCTAATGG	3552
AGGTTGCTTC	AGAAATCAAT	TGAGGTTGAT	TCTGGCAATG	AGCAGTTAGA	GAAGATAAAA	3612
AACAGGGAAA	TCAAATATTC	ACACACACAC	ACACACACAC	ACGTACACTC	ACATGCACAA	3672
GCAAGTGCAT	GCATGCAAAC	CCACACAGAC	TACTTGAAGC	AAAGGCAAGG	TCCAGCCACT	3732
TGAAACATAC	AAATGTGTAC	ATATAGACAG	ACACAGACAA	ACACATACAT	ATCCACATGT	3792
TAAATGGCTG	GAGCAATGTC	AGCCAGCAGG	CTCCATGTAT	TTCACATATG	TACATATATG	3852
CATGTAAATA	AATATTCAGA	TATACACATA	TTCACATGTA	CTGGTGGGTA	GGTGGAATAA	3912
AGTTCCAAAA	AACAGGCCCC	AGGAATTTTA	CACATAATGT	ACAGACATAT	ATAACACTAT	3972
TGGTGGAAGA	ACAAGCTCCA	ACATATTCAG	GGAAGCATTG	CATATACATA	CATATAGATT	4032
TGATGGATGG	AACAAAGTTC	CAACAAATTC	TCACATGAAC	TTTATATATG	TATATACATG	4092
AAAGGCAGCC	TGGTTCCCAG	TTGATCAGAG	GTTTGAAAGC	CCAGTGACCC	TAAAAAAGAT	, 4152
GGTAGCCATT	TAGCCTGATT	CCCAGTAAAC	CAGGCAAGTC	ACTAGCCACA	GCCCTCCATA	4212
GAATTTTGGC	CATCAGTCAC	TTAAGCCCAA	CACCCTCCAC	AGATTAAAGG	AAGTGATTAC	4272
AGGTCACAGG	GACTCAGAAC	ACATTTCCAT	TATGTGACAT	AGTCAAAGAC	TTGGAGACTT	4332
AGCCAATGAA	CTTTCCTTCC	CTGAAACTCC	TCCCTGCAGG	CCAACCTTGA	AAAGAGGGGT	4392
ATGGTTTTAC	TCATCTGCTT	TCAGCCATGA	CAATAAATGA	CTTAAAACAA	TGAAAAAAA	4452
ААААААААА	AAAAA					4467

#### (2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 866 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Met Ser Arg Leu Arg Ala Gly Lys Asn Met Leu Thr Phe Ile Leu Leu 10 Phe Phe Leu Leu Asn Ile Pro Leu Phe Val Pro Ser Phe Ile Tyr Pro 20 25 Arg Cys Phe Trp Ser Met Lys Lys Asn Glu Tyr Gln Asp Arg Asn Leu 35 40 45 Gly Thr Gly Cys Met Phe Phe Ile Leu Ala Val Gln Gln Pro Met Glu 50 · 55 60 Lys Glu Tyr Phe Ser His Ile Ser Asn Ile Gln Thr Pro Thr Glu Asn 70 75 Gln Lys Tyr Pro Leu Thr Leu Ala Phe Ser Met Asn Glu Ile Asn Asn 85 90 Asn Pro Asp Leu Leu Pro Asn Met Ser Leu Ala Phe Thr Phe Ser Glu 100 105 Tyr Ser Cys Tyr Leu Glu Ser His His Lys Arg Leu Phe Asn Phe Ser 115 120 125 Leu Lys Asn His Glu Ile Leu Pro Asn Phe Ile Cys Thr Lys Asp Ile 130 135 140 Lys Cys Gly Val Val Leu Thr Gly Leu Ser Leu Val Thr Thr Val Thr 150 155 160 Leu His Ile Ile Leu Asn Asn Phe Ile Phe Gln Gln Phe Arg Gln Leu 170 165 Thr Tyr Gly His Phe His Pro Ala Leu Cys Asp His Glu Asn Phe Pro 180 185 His Leu Tyr Gln Met Ala Ser Asp Asp Thr Ser Leu Ala Leu Ala Leu 195 200 205 Val Ser Phe Ile Ile His Phe Ser Trp Asn Trp Ile Gly Leu Ala Ile 215 220 Ser Asp Asn Asp Gln Gly Ile His Phe Leu Ser Tyr Leu Arg Arg Glu 230 235 225 Met Glu Lys Asn Thr Val Cys Phe Ala Phe Val Asn Ile Ile Pro Val 245 250 Asn Met Asn Leu Tyr Met Ser Arg Ala Glu Val Tyr Tyr Ser Gln Val .

			260					265					270		
Met	Thr	Ser 275	Ser	Ala	Asn	Val	Val 280	Ile	Ile	Tyr	Gly	Asp 285	Thr	Gly	Asn
Thr	Leu 290	Ala	Val	Ser	Phe	Arg 295	Met	Trp	Asp	Ser	Leu 300	Gly	Ile	Gln	Arg
Leu 305	Trp	Val	Thr	Thr	Ser 310	Gln	Trp	Asp	Val	Thr 315	Pro	Phe	Lys	Lys	Asp 320
Phe	Thr	Phe	Asp	Asn 325	Gly	Tyr	Gly	Thr	Phe 330	Gly	Phe	Gly	His	Arg 335	His
Ser	Glu	Ile	Ser 340	Gly	Phe	Lys	Tyr	Phe 345	Val	Gln	Thr	Leu	Asn 350	Pro	Phe
Lys	Tyr	Ser 355	Asp	Glu	Tyr	Leu	Val 360	Lys	Leu	Glu	Trp	Met 365	Tyr	Val	Asn
-	370				Tyr	375	_	_			380		-		
Asn 385	His	Ser	Leu	Glu	Trp 390	Leu	Met	Thr	His	Thr 395	Phe	Asp	Met	Ala	Ile 400
		_		405	Glu		_		410		_			415	
			420		Thr			425					430		
		435			Asn		440					445			
	450				Thr	455			-	_	460				
465					Lys 470					475					480
				485	Gly				490		-			495	
-			500	_	Gln			505					510		
_		515	_	_	Ile		520					525			_
	530				Arg	535		_			540				
545		_	_		Pro 550	_				555					560
				565	Val				570					575	
			580	_	Ile		_	585	-				590	_	_
		595	· -		Ala		600					605			
	610				Leu	615					620				
625		_			Asn 630	_				635					640
				645	Leu				650					655	
_			660		Leu			665			_		670		_
		675			Val		680	_				685			
	690				Pro	695	_			-	700				
705					11e 710					715					720
				725	Leu				730					735	
			740		Gly			745			-		750	_	
		755		_	Cys		760	_	_			765			
AST	770	rne	inr	nea	Ala	775	neu	ser	wid	ASI1	780	PTO	val	Inr	FIIG

- 142 -

Asn Glu Ala Lys Ser Met Thr Phe Ser Met Leu Val Phe Cys Ser Val 790 795 Trp Val Thr Phe Leu Pro Val Tyr His Gly Thr Lys Gly Lys Val Met 810 Val Ala Val Glu Ile Phe Ser Thr Leu Ala Ser Ser Ala Gly Met Leu 825 830 Gly Cys Ile Phe Ala Pro Lys Cys Tyr Thr Ile Leu Phe Arg Pro Asp 840 845 Arg Asn Ser Leu Gln Met Ile Arg Glu Lys Ser Ser Ser His Thr His 855 860 Ile Leu 865

### (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2916 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence (B) LOCATION: 299...2635

  - (D) OTHER INFORMATION: GOVN5

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CGGCACGAGT TCAACTAGTC ATGTTCAAGA AGGGGCAAAT ACTTTGTTAA TATGCTCTTC	60
GCTTGGACTT TTATCTCTTG CTTTCTGCAG ATTCCAATTA TTTTATGCTC CTACAGAAGC	120
AGCGAGTGCT TAGTCAAGAT GAATTATCGT TTAAAGGGGA AAGGAAATGT GGTGATTGTT	180
GGATTTTTCC CTGCTTTTGC TGTCTACCCC CTCAACAAA CAATTGACTG GTGGATGCTT	240
AAATTCAGCA AAGAATTATG ATTGAGTTTA AGTTGAAGAG CTACCAGTAT ATTTGGCC AT	300
Met	
1	
GAG GTT TGC CAT TGA GGA AAT CAA CAG CAA TCC CCA TCT TTT ACC AAA	348
Arg Phe Ala Ile Glu Glu Ile Asn Ser Asn Pro His Leu Leu Pro Asn	
5 10 15	
CAC AME COM COC AME MOS CAR CAS MAN TO COC ACC ACC ACC ACC	
CAC ATC CCT GGG ATT TGA GAT CAA TAA TGT CCC ACA CGG TCA GAG GTA	396
Thr Ser Leu Gly Phe Glu Ile Asn Asn Val Pro His Gly Gln Arg Tyr 20 25 30	
20 25 30	
CAC TCT GGT CAA ACT TTT TAG CTC ACT TTC AGG GTC TAA TTA TGA CAT	444
Thr Leu Val Lys Leu Phe Ser Ser Leu Ser Gly Ser Asn Tyr Asp Ile	444
35 40 45	
TCC TAA CTA CAT AAG TGC AAG TGA GAG CAA TTC TGC TGC TGT ACT TAC	492
Pro Asn Tyr Ile Ser Ala Ser Glu Ser Asn Ser Ala Ala Val Leu Thr	
50 55 60 65	
AGG ACC ATC GTG GAC AAT ATC TGA ATG CGT AGG GAC ACT CCT GGA TCT	540
Gly Pro Ser Trp Thr Ile Ser Glu Cys Val Gly Thr Leu Leu Asp Leu	
70 75 80	
MM1 (3) 100 MGC 101 GCT T10 T10 T10 T10 T10	
TTA CAA ATT TCC ACA GCT TAC TTT TGG GCC TTT TGA TAG TCT CCT GAG	588
Tyr Lys Phe Pro Gln Leu Thr Phe Gly Pro Phe Asp Ser Leu Leu Ser	
85 90 95	
TGA ACA AAG ACG GTT TTC TTC TCT GTA CCA AGT GGC CCC CAA AGA TAC	636

Glu Gln Arg Arg Phe Ser Ser Leu Tyr Gln Val Ala Pro Lys Asp Thr.

WO 99/00422 PCT/US98/13680

100	105	110	
		AT GCT TCA TTT CCA CTG Met Leu His Phe His Trp 125	
		EA CAA AGG TGC CCA GAC Asp Lys Gly Ala Gln Thr 140	
	Glu Met Asp Lys A	AA TGG AGT CTG CAC AGC Asn Gly Val Cys Thr Ala L55 160	Phe
		FC ATT TTT TAC CAA ATC Ser Phe Phe Thr Lys Ser 175	
	_	TC ATC AAA TGT GAT TAT Ser Ser Asn Val Ile Ile 190	
_		TT AAT AGT AAA TAT TAA Leu Ile Val Asn Ile Lys 205	
		CT GAT CTC ACA GTG GGA Leu Ile Ser Gln Trp Asp 220	
	Tyr Phe Met Val A	GA CTC ATT GCA TGG AGC Asp Ser Leu His Gly Ala 235 240	Leu
		CC TAA TTT TAC AGA TTT Pro Asn Phe Thr Asp Phe 255	
		GA AGA CAC TTA TCT TCA Glu Asp Thr Tyr Leu His 270	
		TT TGT TAA GAA AGA TTG Phe Val Lys Lys Asp Cys 285	
AAT TGT GCA CAA CTG Ile Val His Asn Cys 290	TTT GCC TAA TGC CT Leu Pro Asn Ala S 295	TC CCT GGG GTT CTT GCC Ser Leu Gly Phe Leu Pro 300	TGG 1212 Gly 30
	: Ala Met Ser Glu (	GA GAG TTA CAA TGT ATA Glu Ser Tyr Asn Val Tyr 315 320	Asn
		CA TGA GAT GAT TCT CAA His Glu Met Ile Leu Asn 335	
		AA AAA GAT GGT ATT CTT Lys Lys Met Val Phe Phe 350	
		AG ACA ACT CAT CAA TCA Arg Gln Leu Ile Asn Gln 365	

	TGG AGC Gly Ala 370			Asp									Glu '		1452
5	TGA CAT Asp Ile		Asn												1500
•	GAA AGT Lys Vai							Pro							1548
	CAT ATC Ile Se						, Ala								1596
	ACA GTC Gln Se: 43	r Val			Glu S										1644
	CCA GGA Gln Gl 450			Val									Pro		1692
5	AAA TGA Asn Gl														1740
	AGA AAC Glu Th							Ile			Leu				1788
	TGT GAC Val Th		Leu				p Pro				_			_	1836
	CAT GTC Met Se 51	r Leu			Ser S										1884
	TCT GAA Leu Ly 530												Ala		1932
5	CAG TTA Ser Ty														1980
	GCT CTT Leu Ph							Ser							2028
	CAT TTT Ile Ph		Leu				l Ala								2076
	AAC TAT Thr Il 59	e Thr			Ile A										2124
	TAG AAG Arg Ar 610									Phe					2172
	ATG CAC	CCT	GCT C	CA A	GT T	T TCT	ATC	TGG	AAT	TTG (	GCT (	SAC .	AAC C	CTC .	2220

5	Cys	Thr	Leu	Leu	Gln 630	Val	Phe	Leu	Ser	Gly 635	Ile	Trp	Leu	Thr	Thr 640	Ser	
7										Ser					CAT (		2268
c									Val						CCT 1 Leu		2316
1			Gly							-			Ala		CTT G Leu		2364
(												Phe			TTT ( Phe		2412
5											Phe				Tyr 720		2460
(										Met					TAT (		2508
(									Ile						GTG ( Cys		2556
(			Leu					-					Tyr		CAG ( Arg		2604
(		Thr		TGC : Ala								GCAT	CCTT	ATG	TGCC1	CT T	2656
(	AAGT CCTA FATT	CATA ATGC AGTT	AT TO	GTACA TTTCA	ATTT ACAT ATTG	G AT T AA A TT	CCAG AATA	GGGC TGTG	TAT	TATT	TCT TTT	TTAG CGTC	TAGT TTCC	CA T. TC T	ATATA TCTA	ATATA ATGTA CTTAC ICCAA	2716 2776 2836 2896 2916
			(-)								_						

- (2) INFORMATION FOR SEQ ID NO:42:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 779 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Met Arg Phe Ala Ile Glu Glu Ile Asn Ser Asn Pro His Leu Leu Pro 10 Asn Thr Ser Leu Gly Phe Glu Ile Asn Asn Val Pro His Gly Gln Arg 20 25 Tyr Thr Leu Val Lys Leu Phe Ser Ser Leu Ser Gly Ser Asn Tyr Asp 40 45

Ile Pro Asn Tyr Ile Ser Ala Ser Glu Ser Asn Ser Ala Ala Val Leu .

Thr Gly Pro Ser Trp Thr Ile Ser Glu Cys Val Gly Thr Leu Leu Asp Leu Tyr Lys Phe Pro Gln Leu Thr Phe Gly Pro Phe Asp Ser Leu Leu Ser Glu Gln Arg Arg Phe Ser Ser Leu Tyr Gln Val Ala Pro Lys Asp Thr Phe Leu Thr Pro Gly Ile Val Ser Leu Met Leu His Phe His Trp Asn Trp Val Gly Leu Phe Ile Ile Asp Asp Asp Lys Gly Ala Gln Thr Leu Ser Asp Leu Arg Asn Glu Met Asp Lys Asn Gly Val Cys Thr Ala Phe Val Glu Met Ile Pro Val Ile Lys Gly Ser Phe Phe Thr Lys Ser Trp Lys Asn His Val Gln Ile Leu Glu Ser Ser Asn Val Ile Ile Ile Tyr Gly Asp Ser Asp Ser Leu Leu Ser Leu Ile Val Asn Ile Lys Gln Lys Leu Leu Thr Trp Lys Val Trp Val Leu Ile Ser Gln Trp Asp Val Ser Lys Phe Asp Asp Tyr Phe Met Val Asp Ser Leu His Gly Ala Leu Ile Phe Ser His His Arg Glu Glu Ile Pro Asn Phe Thr Asp Phe Met Gln Lys Tyr Asn Pro Ser Lys Tyr Pro Glu Asp Thr Tyr Leu His Val Leu Trp His Met Tyr Phe Asn Cys Ser Phe Val Lys Lys Asp Cys Lys Ile Val His Asn Cys Leu Pro Asn Ala Ser Leu Gly Phe Leu Pro Gly Asn Ile Phe Asp Met Ala Met Ser Glu Glu Ser Tyr Asn Val Tyr Asn Ala Val Tyr Ala Val Ala His Ser Leu His Glu Met Ile Leu Asn Gln Val Gln Phe Gln Thr His Glu Lys Gly Lys Lys Met Val Phe Phe Pro Trp Gln Leu His Pro Phe Leu Arg Glu Arg Gln Leu Ile Asn Gln Asn Gly Ala Asn Glu Asp Leu Asp Cys Thr Arg Lys Ser His Val Glu Tyr Asp Ile Leu Asn Phe Trp Asn Phe Pro Lys Gly Leu Gly Leu Asn Val Lys Val Gly Thr Phe Ser Pro Ser Ala Pro Lys Glu Gln Lys Leu Ser Ile Ser Ser Asn Met Ile Gln Trp Ala Thr Gly Ser Thr Glu Ile Pro Gln Ser Val Cys Ser Glu Ser Cys His Pro Gly Phe Arg Lys Thr His Gln Glu Gly Arg Val Ala Cys Cys Phe Asp Cys Ile Pro Cys Pro Glu Asn Glu Ile Ser Asn Glu Thr Asp Val Asp Gln Cys Val Lys Cys Pro Glu Thr His Tyr Ala Asn Ile Glu Lys Ile His Cys Leu Gln Lys Thr Val Thr Phe Leu Tyr Tyr Asp Asp Pro Leu Gly Lys Thr Leu Cys Phe Met Ser Leu Gly Phe Ser Ser Leu Thr Ala Ala Val Leu Val Val Phe Leu Lys Asn Arg Asp Thr Pro Ile Val Lys Ala Asn Asn Leu Ala Leu Ser Tyr Thr Leu Leu Ile Thr Leu Met Leu Cys Phe Leu Cys Pro Leu Leu Phe Ile Gly Arg Pro Ser Thr Ala Ser Cys Ile Leu Gln Gln 

PCT/US98/13680

0

- 147 -

WO 99/00422

Asn Ile Phe Gly Leu Leu Phe Thr Val Ala Leu Ser Thr Val Leu Ala 580 585 Lys Thr Ile Thr Val Val Ile Ala Phe Lys Ile Thr Ser Pro Gly Arg 600 595 605 Ile Arg Arg Trp Leu Leu Ile Ser Arg Ala Pro Asn Phe Ile Ile Pro 610 615 620 Leu Cys Thr Leu Leu Gln Val Phe Leu Ser Gly Ile Trp Leu Thr Thr 630 635 Ser Pro Pro Phe Ile Asp Lys Asp Ala His Ser Glu His Gly His Ile 645 650 Ile Ile Ile Cys Asn Lys Gly Ser Ala Val Ala Phe His Cys Asn Leu 665 660 Gly Tyr Leu Gly Ala Leu Ala Leu Val Ser Tyr Phe Met Ala Phe Leu 675 680 Ser Arg Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu Ala Phe 695 700 Ser Met Leu Val Phe Cys Ser Val Trp Val Thr Phe Leu Pro Val Tyr 710 715 720 His Ser Thr Lys Gly Lys Asn Met Val Ala Met Glu Val Phe Ser Ile 725 730 735 Leu Ala Ser Ser Thr Ser Leu Leu Gly Ile Ile Phe Ala Pro Lys Cys 745 740 750 Tyr Leu Ile Leu Leu Arg Pro Glu Arg Asn Ser Leu Ser Tyr Ile Arg 755 760 Asp Lys Thr Tyr Ala Lys Ser Ile Lys Pro Ser 775

## (2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3307 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence
  - (B) LOCATION: 112...1761
  - (D) OTHER INFORMATION: GOVN6

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

	GTCTTCTT CTTCTTCCTT A	
<b></b> -	 TGT TCC TTC ATC CTT ( Cys Ser Phe Ile Leu ( 15	
	TTC AAC CAG ACT CTG . Phe Asn Gln Thr Leu . 30	
	 GCT TTG GCA TTG GCC Ala Leu Ala Leu Ala 45	
	CTT TTA CCA AAT ATG Leu Leu Pro Asn Met 60	

WO 99/00422 PCT/US98/13680

																_
_					TTG Leu	_										357
					AAT Asn											405
					ACT Thr											453
					AGT Ser 120											501
					AAG Lys											549
					AAG Lys											597
					CAA Gln											645
					TTT Phe											693
					AAA Lys 200											741
					ATT Ile											789
					ATG Met											837
_					ATG Met											885
					GGG Gly											933
					AAT Asn 280											981
					GTA Val											1029
					TGT Cys											1077
TCA	TTG	GAA	TGG	TTA	ATG	GAG	CAG	ACA	TTT	GAC	ATG	GTC	TTT	AGT	GAT	1125

i	Ser	Leu	Glu 325	Trp	Leu	Met		Gln 330	Thr	Phe	Asp	Met	Val 335	Phe	Ser	Asp	
												ATG Met 350					1173
1												GCA Ala					1221
												TCC Ser					1269
												ATT Ile					1317
												ACT Thr					1365
												TTC Phe 430					1413
												ATG Met					1461
												ACT Thr					1509
												GCA Ala					1557
												AAT Asn					1605
												GCC Ala 510					1653
												AGC Ser					1701
												TTT Phe					1749
			TGT Cys		TAG	GTC:	PTT (	etgai	AGCA	CC A	rgaci	ACTC(	C TA	rtgt(	GAAG	GCCAA	1806
	TTT( TGT) CAAJ CAT	CTTCI ATTCI AGTCI FATC	ACT (ACA I	GCCI GTGG( AACC( ATAT(	ATCC TAT AGG TTC	TA ACT C'AA GE	CAGA FACA AAGG' GTTT	GCAA( ATTT ITGA( CAAT(	C CTC I GGC G AAI G TA'	CAAA ACTT CTCT	CTTA AACA CCTA GTGT	CAGO ATCA GTA GCA	CAAA' ACTG' I'TGG( ATCT(	rca ( rgg ' gta ( ggc '	CATT TTCT( CACT( TAGC	CTCATT IGGAAT IGCTTT CAACTA AGTTTC ITGCAA	1866 1926 1986 2046 2106 2166

CAAAGGCTCA GTAACTGCAT TCTACTGTGT CCTGGGATAC TTGGCCTGCT TGGCACTTGC 2226 AAGCTTCACT GTGGCTTTCT TGGCAAAGAA TCTGCCAGAC ACATTCAATG AAGCCAAGTT CTTGACCTTC AGCATGCTGG TGTTCTGCAG TGTCTGGGTC ACCTTCCTCC CTGTCTACCA CAGCACCAAG GGCAAGATCA TGGTTGCTGT GGAGATATTC TCCATTTTGG CATCCAGTGC 2406 AGGGATGCTT GGATGCATCT TTGCACCCAA GATTTACATC ATTTTAATGA GACCAGAGAG 2466 AAATGCTATC CAAAAGATCA GGGAGAAATC ATATTTCTGA ACAAATTATT TCAGAATTTC 2526 TATCAAATGT AAACATGGTA TATACCCATC AAATATTGTG TTACAGTGCA TGTATCTAGT TTTAGAATCA CTCTCACTGG TACCCCTAGT GATGTCTAGA AATATCATAT CTACCAATCT 2646 TGAATACATT GTCCATAAAA TCTTGTACAT ATTCACTAGC TTAGTTTCCT GTGGGAGAAC TAAAATTCTC AAATTATTAT TACAATTTTA TTCATAATTT TGCTCTCATG GCAAATCAGA ACTCATTTTC TAATTTCCAG TAACAACACA TACATGACAG AATACTGATT TTCAGCTATT CTTTAAGCTA TTGGCCAATA GACTAAGGTG GAAATGTTCT TTTTCTTTCT GAAACACAAA 2886 AATATTATAT CATATAATAC ACAGAAGTCA GGGACCCCTA TGGATGAATT AGGGAATAGT TGGAAGAAGC TGGCTGAGTA GAAGGGTGAC CCATAGGAAG ACCAGCAGTC TCACCTAACA AGGACAACCA AGATCTTGCT GACACTGAAT CACTTGCTAG GCAGTTGATT TGAGGCCCCT GACACATATC AAGCATAGGA CTACATTGGC TGGCCTCAGT GGGAGAAGAC AACCTAACCC 3126 CCTAGAGACT TGAGGCCCCA GGCTAAGGGG AGGTTGGGGG TTTTGAAAGT TGGGGATATT 3186 ATCTTGGAGT TGGGGAGGG TATGGGATGA AGAAGAGTCA GGAGGCAGGT GCTGGTTGGA 3246 GTATAATGAC TGGACTGTAA ATAAAAGACT AACAACCAAA AATAAATAAA ATAACTTAAA 3306 3307

#### (2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 550 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met Lys Leu Arg Asp Lys Asp Leu Ser Ile Thr Cys Ser Phe Ile Leu 10 Glu Ala Val Gln Met Pro Thr Glu Asn Asp Tyr Phe Asn Gln Thr Leu 25 3.0 20 Asn Ile Leu Lys Thr Thr Lys Asn His Lys Tyr Ala Leu Ala Leu Ala 40 Phe Ser Ile Asp Glu Ile Asn Arg Asn Pro Asp Leu Leu Pro Asn Met 55 60 Ser Leu Ile Ile Lys Tyr Pro Leu Gly Leu Cys Asp Gly Gln Thr Thr Leu Pro Thr Pro Tyr Leu Phe Asn Glu Ile Tyr Phe Arg Pro Ile Pro 90 Asn Tyr Phe Cys Asn Glu Glu Thr Met Cys Thr Phe Leu Leu Thr Gly 105 Pro His Trp Ile Thr Ser Tyr Ser Phe Trp Ile His Leu Asn Ile Phe 120 Leu Ser Pro Ser Met Asn Pro Lys Asp Thr Ser Leu Ala Leu Ala Met 130 135 140 Val Ser Phe Leu Leu Tyr Phe Lys Trp Asn Trp Val Gly Leu Val Ile 150 155 Ser Asp Asp Asp Gln Gly Asn Gln Phe Leu Ser Glu Leu Lys Lys Glu
165 170 175 Ser Lys Ile Lys Glu Ile Cys Phe Ala Phe Val Ser Met Leu Ala Ile 185 Asp Glu Ile Ser Phe Tyr His Lys Thr Glu Met Tyr Tyr Asn Gln Ile 200 205 Val Met Ser Ser Thr Asn Val Ile Ile Ile Tyr Gly Lys Thr Glu Ser 215 210 220 Ile Ile Glu Leu Ser Phe Arg Met Trp Glu Ser Pro Val Ile Gln Arg 230 235 Ile Trp Val Thr Thr Lys Glu Met Asn Phe Pro Thr Ser Lys Arg Asp

PCT/US98/13680

- 151 -

250 245 Leu Thr His Asp Thr Phe Tyr Gly Thr Leu Thr Phe Leu His Ser His 265 260 270 Gly Glu Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Trp Tyr His Leu 275 280 285 Arg Ile Thr Asp Leu His Leu Val Met Pro Glu Trp Lys Tyr Phe Asn 295 300 290 Tyr Glu Ala Ser Ala Ser Asn Cys Lys Ile Leu Lys Asn Tyr Ser Ser 310 315 Ser Ala Ser Leu Glu Trp Leu Met Glu Gln Thr Phe Asp Met Val Phe 330 325 335 Ser Asp Gly Ser Arg Asp Ile Tyr Asn Ala Val Asn Ala Met Ala His 340 345 350 Ala Leu His Glu Met Asn Leu His Leu Val Asp Asn Gln Ala Ile Asp 360 365 Asn Gly Lys Gly Ala Ser Ser His Cys Phe Lys Ile Asn Ser Phe Leu 375 380 Arg Lys Thr His Phe Thr Asn Pro Leu Gly Asp Arg Val Ile Met Lys 390 395 Glu Arg Glu Ile Leu Gln Glu Asp Tyr Asn Ile Phe His Thr Trp Asn 405 410 Phe Ser Gln His Ile Gly Phe Lys Val Lys Ile Gly Lys Phe Ser Pro 425 Tyr Phe Pro His Gly Arg His Phe His Leu Tyr Val Asp Met Ile Glu 440 Leu Ala Thr Gly Ser Arg Lys Met Pro Ser Ser Val Cys Thr Glu Asp 450 455 460 Cys Ser Pro Gly Tyr Arg Arg Phe Trp Lys Glu Gly Met Ala Ala Cys 470 475 Cys Phe Val Cys Ser Pro Cys Pro Glu Asn Ala Ile Ser Asn Glu Thr 485 490 Asn Met Asp Gln Cys Val Asn Cys Pro Glu Tyr Gln Tyr Ala Asn Thr 500 505 510 Lys Arg Asp Lys Cys Ile Gln Lys Asn Val Met Phe Leu Ser Tyr Lys 515 520 525 Asp Pro Leu Gly Asp Asp Ser Cys Leu His Ser Leu Leu Phe Leu Cys 535 Ile Asn Ser Cys Cys Thr

### (2) INFORMATION FOR SEQ ID NO:45:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3938 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence
  - (B) LOCATION: 46...2424
  - (D) OTHER INFORMATION: GOVN7
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGC CCAGGTTTAA GGCTGGAAAA AATATGTTCA TTTTG ATG ATA GTA TTC 57

Met Ile Val Phe

TTT CTC CTC AAC ATT CCA CTT CTC ATG GCA AAT TCC GTT GAT CCC AGG
Phe Leu Leu Asn Ile Pro Leu Leu Met Ala Asn Ser Val Asp Pro Arg
5 10 15 20

WO 99/00422 PCT/US98/13680

																-
														TTA Leu 35		153
														GAG Glu		201
														TAC Tyr		249
														AGG Arg		297
														TTG Leu	_	345
														TTT Phe 115		393
														TCA Ser		441
														ATT Ile		489
														CCT Pro		537
														CAG Gln		585
ACC Thr	CCA Pro	AAG Lys	GAT Asp	ACA Thr 185	TCA Ser	CTA Leu	GCA Ala	TTG Leu	GCA Ala 190	ATG Met	GTC Val	TCT Ser	TTC Phe	ATA Ile 195	CTT Leu	633
		Asn	Trp	Asn	Trp	Val	Gly	Leu	Val	Leu		Asp	Asn	Asp	GAA Glu	681
															GAA Glu	729
														TCA Ser	TCC Ser	777
ATG Met 245	Lys	AAA Lys	ACT Thr	GAC Asp	ATG Met 250	TAC Tyr	TAC Tyr	AAC Asn	CAA Gln	ATT Ile 255	Val	ATG Met	TCA Ser	ACC Thr	GCA Ala 260	825
					Tyr					Ser				CTG Leu 275		873
TTC	AGA	ACA	TGG	ACA	TCT	CCA	GTC	ATA	CAG	AGG	ATA	TGG	GTT	ACC	AAA	. 921

WO 99/00422 PCT/US98/13680 - 153 -

																-
Phe	Arg	Thr	Trp 280	Thr	Ser	Pro	Val	Ile 285	Gln	Arg	Ile	Trp	Val 290	Thr	Lys	
			TAT Tyr													969
			ACT Thr													1017
			TTT Phe													1065
			AAG Lys													1113
			AAA Lys 360													1161
			GAA Glu													1209
			AAT Asn													1257
			CAA Gln													1305
			TGC Cys													1353
			TTT Phe 440													1401
			TAT Tyr						_				_			1449
AGG Arg	ATT Ile 470	AAG Lys	GTG Val	AAG Lys	ATA Ile	GGG Gly 475	CAG Gln	TTC Phe	AGC Ser	CCA Pro	TAT Tyr 480	TTT Phe	CCA Pro	CAT His	GGT Gly	1497
	Gln		CAC His													1545
			CCT Pro													1593
			TGG Trp 520	Lys					Ala							1641
															TGG Trp	1689

WO 99/00422 PCT/US98/13680

- 154 -

	535		540	•			545				
		CAC CAT His His									1737
		ATA TTA Ile Leu 570									1785
		ATT GGC Ile Gly 585		Asn A							1833
		GGA ATT Gly Ile									1881
		ACT GTG Thr Val				Val					1929
		AAC TTC Asn Phe									1977
		CTG TTG Leu Leu 650									2025
		TTT GTT Phe Val 665		Asp G							2073
		TGC AAC Cys Asn									2121
		GCC TTC Ala Phe									2169
		CTG CCT Leu Pro									2217
		GTG TTC Val Phe 730									2265
		AAG GGC Lys Gly 745		Met V							2313
ATT TTG Ile Leu	ACA TCC Thr Ser 760	AGT GCA Ser Ala	GGG ATG Gly Met	CTT C Leu C 765	GGA TGC Gly Cys	GTC Val	TTT Phe	GCA Ala 770	CCC Pro	AAA Lys	2361
		TTA ATG Leu Met									2409
	TCA CGT Ser Arg	TTC TAAA	CAGATA 1	rttta(	GAAAT T	CTGTC	CAAA:	GT?	ACAG!	rtgt t	2465

ATATACCCAC CAAATATTTG GTTACAGTGC ATAAATCTAG TTTTAGAACT CTCACTAGTT CCTCTAATGA TATCTAGAAA TATTGTATCT ACCAATCTTA CATTCATTAT CCATAAAATC CTGCACTCAT TCACTTGTTT GTTCTACTCT GTGAGAAATA TAATTCCCAA TGTAGTATTA 2645 AATTTTTTCT AAAAATTTTG CTTTAATTGA CATTTTTCC CTTATAACTT CAAGTACATT TGATAAGGCA TTTGAATCTA TAACCTTTTA TACAATAAGA TCCAGGACAG ACAGGATTAC ACATAGAAAC CGTCTATCGA ATCAAACAAT CAATCAGACT AAAAAACAAA GAATCAACAA AGATAACATC AGAATACATT ATCTGATTTC CAGTAGAAGC ACATATGTGA CAGAATACTG TCTGTTTTTA TAGTTCCTCT TCAAGCTATT GTATTGGTCA GCAGTCTAAG GTAGAAGTTT TTTTGTCACA AACACAAAAA TATTGTATCC AACAATGGAC AGAATCCAGT GAGCACCCTG 3005 TTCAAATTTG GAGATAGTTG GAATATCATG AAAAAGAGGG TGACCCATAA GAATACCAGC ATTCTCAACT AACCTGGACA ACCACGAATT TGAGCTGCTG ACCAGGCAGC ATACATAAGC 3125 TGATATGAGG CTCCCAGCAC AGATGCAACA TAGGGCTGCC TGGTCTGGCC TCAGTGGAAG AAGACACATT TAAACCACAA GAGACAGGAG TCACAAGGGA TTGGGAAGGT GTGATGGTTT GCATATGCTT GGCTCAGGAA GTGGCACTAT TAGAAGGTGT AGACTTGATG GAGGAATTTG TCACTGTAGG GGTGGGCTTG GAGATCCACC TCATAGCTGC CTGGGGATGC TCAGTCTGTT CCTGGCTTCC TTCAGGTGAA GATATAGAAC TCAGATCCTC CTTCACCAAG CCTGCCTGGA 3425 TGCTGTGATG CTGCCATGCT CCGACCTTGA TGATAATGGA CTGAACCTCT GAACATGTAA GCTGGCTCCA ATTAAAGGTT GTCCTTTATA AAACTTCCAT TGATCACAGT GTCTGTACAT AGCAATAAGA CCCAAACTAA GACAGAAGGT GTGTGGATTG GGGAAGTGGG GATTTCCTCT TGGAGGTGGG GAAGTAGTCA AAGATTAAAT TGGGAAGGGG ATAATGAGTA CACCGTAAAA AGTATTAAAG AATAAAATAC TAAAAAATTA ATTAAATAGG ATTGTGAATA TATTAACATG 3725 CTATTATATT ATAGTTCTGG AAGGGATAGG TAAAACTCCT GATGGTGGTT TGTACCTAAT TTTTCTTAGA GCTTGCCCTT TGTATTCAGT TGTGATTGAA ATCCTGGGCT CACAAAATTC TAGTACTATG GATATGGAGG CAGATACTTT GATTACGCTG CTTCCTAGAA ATAAATTTTC 3905 САААААССАА ААААААААА ААААААААА ААА

### (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 793 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEO ID NO:46:

Met Ile Val Phe Phe Leu Leu Asn Ile Pro Leu Leu Met Ala Asn Ser 5 10 Val Asp Pro Arg Cys Phe Trp Lys Ile Asn Leu Asn Glu Val Lys Asp 20 25 Ile Asp Leu Asp Thr Ser Cys Tyr Phe Ile Leu Glu Ala Val Gln Leu 40 Pro Met Glu Lys Asp Tyr Phe Asn Gln Thr Leu Asn Val Leu Lys Thr 55 Thr Lys Tyr Asn Arg Tyr Ala Leu Ala Leu Ala Phe Thr Met Asp Glu Ile Asn Arg Asn Pro His Ile Leu Pro Asn Met Ser Leu Ile Ile Lys His Thr Leu Gly His Cys Asp Gly Asn Ile Pro Leu Arg Leu Leu Asn 105 110 Gln Ile Phe Tyr Met Pro Phe Pro Asn Tyr Gly Cys Asn Glu Glu Thr 120 125 Met Cys Ser Phe Met Leu Met Gly Pro Asn Leu Trp Pro Ser Val Asp 130 135 140 Phe Phe Ile His Leu Asn Ile Leu Phe Pro His Phe Leu Gln Ile Ser 150 155 Phe Gly Pro Phe His Ser Ile Phe Ser Asp Asn Glu Gln Phe Pro Tyr 165 170 Ile Tyr Gln Met Thr Pro Lys Asp Thr Ser Leu Ala Leu Ala Met Val 180 185 190 Ser Phe Ile Leu Tyr Phe Asn Trp Asn Trp Val Gly Leu Val Leu Ser 195 200

Asp Asn Asp Glu Gly Asn Gln Phe Leu Thr Glu Leu Lys Lys Glu Thr His Asn Thr Glu Ile Cys Phe Ala Phe Val Asn Met Met Ala Ile Asn Glu Asn Ser Ser Met Lys Lys Thr Asp Met Tyr Tyr Asn Gln Ile Val Met Ser Thr Ala Asn Val Ile Ile Ile Tyr Gly Glu Arg Pro Ser Ile Ile Glu Leu Cys Phe Arg Thr Trp Thr Ser Pro Val Ile Gln Arg Ile Trp Val Thr Lys Ser Glu Leu Tyr Phe Pro Thr Ser Lys Arg Asp Leu Ser His Gly Thr Phe Tyr Gly Thr Leu Ala Phe Gln Gln His His Asp Val Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Trp Tyr His Leu Lys Ser Met Asp Leu Tyr Leu Leu Lys Pro Glu Trp Gly Phe Phe Glu Tyr Glu Thr Ser Ala Ser Tyr Cys Lys Ile Leu Met Ser Asn Ser Ser Asn Val Ser Leu Glu Trp Leu Met Glu Gln Lys Phe Asp Ile Ala Phe Asn Asp Asn Ser His Ser Ile Tyr Asn Ala Val Tyr Ala Met Ala His Ala Leu His Glu Lys Asn Leu Lys Gln Ile Asp Asn Gln Glu Ile Ser Tyr Gly Lys Gly Ala Ser Thr His Cys Leu Lys Leu His Ser Phe Leu Arg Thr Ile His Phe Thr Asn Pro Phe Gly Glu Arg Val Ile Met Lys Glu Arg Val Arg Val Gln Glu Asp Tyr Asp Ile Val His Leu Gln Asn Cys Ser Gln His Leu Arg Ile Lys Val Lys Ile Gly Gln Phe Ser Pro Tyr Phe Pro His Gly Gly Gln Phe His Leu Tyr Glu Asp Met Ile Asp Leu Ala Thr Gly Ser Arg Lys Met Pro Leu Ser Met Cys Ser Ala Asp Cys Arg Pro Gly Tyr Arg Lys Phe Trp Lys Glu Gly Met Ala Ala Cys Cys Phe Val Cys Ser Pro Cys Pro Asp Asn Glu Ile Ser Asn Glu Thr Thr Val Val Leu Trp Val Phe Val Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Ile Leu Ile Met Ser Leu Met Phe Cys Phe Leu Cys Ser Phe Phe Phe Ile Gly His Pro Asn Arg Gly Thr Cys Ile Leu Gln Gln Ile Thr Phe Gly Ile Val Phe Thr Val Ala Val Ser Thr Val Leu Ala Lys Thr Ile Thr Val Leu Leu Ala Phe Gln Val Thr Asp Thr Gly Arg Lys Leu Arg Asn Phe Leu Val Ser Gly Thr Pro Asn Tyr Ile Ile Pro Ile Cys Ser Leu Leu Gln Cys Thr Leu Cys Ala ¹¹650 Ile Trp Leu Ala Val Ser Pro Pro Phe Val Asp Ile Asp Glu His Ser Glu His Gly His Ile Ile Ile Val Cys Asn Lys Gly Ser Val Met Ala Phe Tyr Cys Val Leu Gly Tyr Leu Ala Phe Leu Ala Leu Gly Ser Phe Thr Met Ala Phe Leu Ala Lys Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe Cys Ser Val Trp Ile Thr.

Dhe	T.en	Pro	Val	725 Tvr	His	Ser	Thr	Lvs	730 Glv	Ara	Val	Met	Val	735 Ala	Val
F 11C	DCG		740	-1-				745	,	3			750		
Glu	Ile	Phe 755	Ser	Ile	Leu	Thr	Ser 760	Ser	Ala	Gly	Met	Leu 765	Gly	Сув	Val
Phe	Ala 770	Pro	Lys	Ile	Tyr	Ile 775	Ile	Leu	Met	Lys	Pro 780	Glu	Arg	Ile	Leu
Ser 785	Lys	Arg	Gln	Glu	Lys 790	Ser	Arg	Phe							

# (2) INFORMATION FOR SEQ ID NO:47:

13	) SECTIENCE	CHARACTERISTICS:
ıı	) DECUENCE	CHARACIERISTICS:

- (A) LENGTH: 3359 base pairs
  (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence(B) LOCATION: 59...2452(D) OTHER INFORMATION: GOVN13C

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGCACGAGC ACAGTCCACT CTGTCAGGGT TTAAGGCAGG AAAAACATGC TCATTTTG AT Met 1	60
GGT AAT ATT CTT CCT TCT CAA CAT TCC ATT TCT CCT GGC AAA TTT CAT Val Ile Phe Phe Leu Leu Asn Ile Pro Phe Leu Leu Ala Asn Phe Met 5 10 15	108
GGA TCC CAG ATG CTT TTG GAA AAT AAA TTT GAA TGA AAT CAA GGA TGA Asp Pro Arg Cys Phe Trp Lys Ile Asn Leu Asn Glu Ile Lys Asp Glu 20 25 30	156
AGT CCT TGG GAT GAC TTG TTC CTT CAT CCT TGA AAC AGT TCA GAA GAC Val Leu Gly Met Thr Cys Ser Phe Ile Leu Glu Thr Val Gln Lys Thr 35 40 45	204
TAT GGA CAA AGA TTA TTT CAA CCA GAC TCT GAA TGT CCT AAA TAC AAC Met Asp Lys Asp Tyr Phe Asn Gln Thr Leu Asn Val Leu Asn Thr Thr 50 55 60 65	252
TAC AAA CCA CAA ATA TGC CTT GGC ATT GGC CTT TAC AGT GGA TGA AAT Thr Asn His Lys Tyr Ala Leu Ala Leu Ala Phe Thr Val Asp Glu Ile 70 75 80	300
CAA CAG GAA TCC TGA TCT TTT ACC AAA TAT GTC TCT GAT TAT AAA ATA Asn Arg Asn Pro Asp Leu Leu Pro Asn Met Ser Leu Ile Ile Lys Tyr 85 90 95	348
CAA TTT GGG TCA TTG TGA TGG AAA AAC TGT AAC AAC TCT ATC CGA TTT Asn Leu Gly His Cys Asp Gly Lys Thr Val Thr Thr Leu Ser Asp Leu 100 105 110	396
ATT TAA TCC AAA TAA TCA TCT CCA TTT CCC CAA TTA TT	444
AGG GAT TAT GTG TTT GGT TCT GCT TAC AGG ACC ACA TTG GAG AGC ATC .	492

Gly Ile Met Cys Leu Val Leu Leu Thr Gly Pro His Trp Arg Ala Ser 130 135 140 14	
TTT ATA TCT CTG GAT ATC CGT GTA TGT CTA CCT GTC TCC ACA TTT CCT Leu Tyr Leu Trp Ile Ser Val Tyr Val Tyr Leu Ser Pro His Phe Leu 5 150 155 160	540
TCA GCT TTC CTA TGG ACC TTT CTA CTC CAT CTT CAG TGA TAA TGA ACA Gln Leu Ser Tyr Gly Pro Phe Tyr Ser Ile Phe Ser Asp Asn Glu Gln 165 170 175	588
ATA TCC TTA TCT CTA TCA GAT GGG CCC AAA GGA CTC ATC ACT AGC ATT Tyr Pro Tyr Leu Tyr Gln Met Gly Pro Lys Asp Ser Ser Leu Ala Leu 180 185 190	636
GGC AAT GGT CTC CTT CAT AAT TTA CTT CAA GTG GAA CTG GGT TGG GCT Ala Met Val Ser Phe Ile Ile Tyr Phe Lys Trp Asn Trp Val Gly Leu 195 200 205	684
ATT TAT CTC AGA TGA TGA TCA AGG CAA TCA ATT TCT CTC AGA GTT GAA Phe Ile Ser Asp Asp Asp Gln Gly Asn Gln Phe Leu Ser Glu Leu Lys 210 225 220	732
AAA AGA GAG CCA AAC CAA GGA TAT TTG CTT TGC CTT TGT GAA CAT GAT Lys Glu Ser Gln Thr Lys Asp Ile Cys Phe Ala Phe Val Asn Met Ile 230 235 240	780
ATC AGT CAG TGA TGT TTC ATA CTA TCA TAA AAC TGA AAT GTA CTA CAA Ser Val Ser Asp Val Ser Tyr Tyr His Lys Thr Glu Met Tyr Tyr Asn 245 250 255	828
CCA AAT TGT GAT GTC ATC CAC AAA GGT TAT TAT CAT TTA TGG GGA AAC Gln Ile Val Met Ser Ser Thr Lys Val Ile Ile Ile Tyr Gly Glu Thr 260 265 270	876
AAA CAG TAT TAT TGA ATT GAG CTT CAG AAT GTG GTC ATC TCC AGT TAA Asn Ser Ile Ile Glu Leu Ser Phe Arg Met Trp Ser Ser Pro Val Lys 275 280 285	924
ACA GAG AAT ATG GGT CAC CAC AAA ACA ATT TGA TTG CCC TAC CAG TAA Gln Arg Ile Trp Val Thr Thr Lys Gln Phe Asp Cys Pro Thr Ser Lys 290 295 300 30	972
GAG AGA CTT AAC TCA TGG CAC ATT CTA TGG GAC CCT TAC ATT TCT ACA Arg Asp Leu Thr His Gly Thr Phe Tyr Gly Thr Leu Thr Phe Leu His  310 320	1020
CCA CTA TGG TGA GAT TTC TGG CTT TAA AAA TTT TGT ACA GAC ACG GTA His Tyr Gly Glu Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Arg Tyr 325 330 335	1068
CAA TCT CAG AAG CAC AGA TTT ATA TCT AGT AAT GCC AGA GTG GAA ATA Asn Leu Arg Ser Thr Asp Leu Tyr Leu Val Met Pro Glu Trp Lys Tyr 340 345 350	1116
TTT TAA CTA TGA AGC CTC AGC ATC TAA CTG TAA AAT ACT GAG AAA CTA Phe Asn Tyr Glu Ala Ser Ala Ser Asn Cys Lys Ile Leu Arg Asn Tyr 355 360 365	1164
TTT ATC CAA TAT CTC ACT GGA ATG GCT AAT GGA ACA GAA ATT TGA CAT Leu Ser Asn Ile Ser Leu Glu Trp Leu Met Glu Gln Lys Phe Asp Met 370 375 380 38	1212
GTC ATT TAG TGA TTA TAG TCA CAA CAT ATA CAA TGC TGT ATA TGC CAT Ser Phe Ser Asp Tyr Ser His Asn Ile Tyr Asn Ala Val Tyr Ala Ile	1260

5	390	395	400	
			TGA AAA TCA GGC 1 Glu Asn Gln Ala 415	1308
			GAA GCT AAA CTC u Lys Leu Asn Ser 430	1356
			GAA CAG AGT AAT y Asn Arg Val Ile 5	1404
			TAT TGT TCA CAT in Ile Val His Met 46	1452
			GAT AGG ACA ATT 'S Ile Gly Gln Phe 480	1500
			ATA TGT AGA CAT u Tyr Val Asp Met 495	1548
			CTC AGT GTG CAG Fr Ser Val Cys Ser 510	1596
			GGA GGA AAT GGC GB Glu Glu Met Ala 5	1644
			TGA AAT TTC TAA n Glu Ile Ser Asn 54	1692
			CCA TGA CAC TCC s His Asp Thr Pro 560	1740
	Asn Asn Arg Ile		ATT AAT CGT GTC u Leu Ile Val Ser 575	1788
		Phe Phe Phe Il	TGG CTA TCC TAA e Gly Tyr Pro Asn 590	1836
			S AAT CTT CTT TAC Ly Ile Phe Phe Thr D5	1884
			TGT GGT TCT GGC r Val Val Leu Ala 62	1932
			CCTT TTT GGT ATC le Phe Leu Val Ser 640	1980
	Tyr Ile Ile Pro		r ATT GCA ATG TAT eu Leu Gln Cys Ile 655	2028

TCT GTG TGC AAT CTG GCT AGC AGT TTC TCC TCC CTT TGT TGA TAT TGA Leu Cys Ala Ile Trp Leu Ala Val Ser Pro Pro Phe Val Asp Ile Asp 660 665 670	2076
TGA ACA CTC TGA GCA TGG CCA CAT CAT CAT TGT GTG CAA CAA GGG CTC Glu His Ser Glu His Gly His Ile Ile Val Cys Asn Lys Gly Ser 675 680 685	2124
CAT TAC TGC ATT CTA CTG TGT CCT GGG ATA CTT GGC CTG CCT GGC CTT  Ile Thr Ala Phe Tyr Cys Val Leu Gly Tyr Leu Ala Cys Leu Ala Phe 690 695 700 70	2172
TGG AAG CTT CAC TAT AGC TTT CTT GGC AAA GAA CCT GCC TGA CAC ATT Gly Ser Phe Thr Ile Ala Phe Leu Ala Lys Asn Leu Pro Asp Thr Phe 710 715 720	2220
CAA CGA AGC CAA GTT CTT GAC CTT CAG CAT GCT AGT GTT CTG CGC TGT Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe Cys Ala Val 725 730 735	2268
CTG GGT CAC CTT CCT CCC TGT CTA CCA TAG CAC CAA GGG CAA GGT CAT Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys Val Met 740 745 750	2316
GGT TGC TGT GGA GAT CTT CTC CAT CTT GGC ATC TAG TGC AGG GAT GCT Val Ala Val Glu Ile Phe Ser Ile Leu Ala Ser Ser Ala Gly Met Leu 755 760 765	2364
GGG ATG CAT CTT TGC ACC CAA AGT TTA CAT CAT TTT AAT GAG ACC AGA Gly Cys Ile Phe Ala Pro Lys Val Tyr Ile Ile Leu Met Arg Pro Asp 770 785 780 78	2412
CAG AAA TTC GAT CCA CAA AAT CAG GGA GAA ATC ATA TTT C TGAAAAGGTA Arg Asn Ser Ile His Lys Ile Arg Glu Lys Ser Tyr Phe 790 795	2462
THE STATE OF THE S	2522
TTTCAGGAAT TCTGTCAAAT GTAAAGTTGA TACATACACC CCAAATATTT AGTTACAGAG	2582
CATATATCTA GTTTTAGAAT CACTCTCACT GGTTCCTCTA GTTAAGCATA GAAGTACCAT ATGTACTGAT CTTGCATATG TTGTCTATAA AATCTTACAA TCATTCATTT GCTTAGTATC	2642
TTCTGGAAGA AGTAAAATTT TCAAATAACT AGTACAATTT TATTCATTAT TTTGCTTTCA	2702
TGAGGATTT CCCCTGGTAA CTTCAAATAA ATTTTATAAG TCAGTTGAAT ATATAACCTT	2762
ACATAGAAAG TGAGTTCTAG GACAGACAGG GATTATACAT AGAAACAAAC TAACTAAAAA	2822
ACATAGAAAG TGAGITCTAG GACAGACAGG GAITATACAT AGAAACAAAC TAACTAAAAA TCAACAAAGA TGAAATCAGA ACACATTTTC TTATTTCCAG TAGGAACACA TACTTGACAG	2882
ATACTGTCT TTTTTTCAGC TGCTCTTTAA GATATTGGCC AATAGTCTAA GCTGAAAATG	2942
TTCTTTATCT ACTCTCAAAT ACAAAAATAT TATATCCAAC AATGGACAGA ATCTGAGAAC	3002
TCCTGTGGTT GAGTTAGGGA ATAGTTGGAA GATACTGAGA AGGAGGTGAC CCATAGGAAT	3062
ACAAAGCAGT CTCAACTAAC CTGGACAACC AAGGTCCCTC AGACACTGAG CCACTAACAA	3122
GTCAGCCTAC TCCAGCTGTT ATGAGGCCCC CAAAACATAT GCAACATAGG ATTGCCTGGT	3182
CCAGCCTCAG CAAGAGAATA CACACCTAAC CACAGAGAGA CTTCCCCAAG GGATTGGGGA	3242
GGTCTGGGGT TTGGAGAGTT GCGGATTGTC CCTTGATGAT TGGAAGGAGG TATTGGATGA	3302
GAATGAATCA GGGGGAAGAC TAGGAAGGGG ATAATGATGG AACTGTAAAA AAAAAAA	3359
CHRISTIAN GOOGRAGIC INCOMPOSES RIGHTONION INSCIONANT SERVICE.	

- (2) INFORMATION FOR SEQ ID NO:48:
- (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 798 amino acids
  (B) TYPE: amino acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Met Val Ile Phe Phe Leu Leu Asn Ile Pro Phe Leu Leu Ala Asn Phe Met Asp Pro Arg Cys Phe Trp Lys Ile Asn Leu Asn Glu Ile Lys Asp Glu Val Leu Gly Met Thr Cys Ser Phe Ile Leu Glu Thr Val Gln Lys Thr Met Asp Lys Asp Tyr Phe Asn Gln Thr Leu Asn Val Leu Asn Thr Thr Thr Asn His Lys Tyr Ala Leu Ala Leu Ala Phe Thr Val Asp Glu Ile Asn Arg Asn Pro Asp Leu Leu Pro Asn Met Ser Leu Ile Ile Lys Tyr Asn Leu Gly His Cys Asp Gly Lys Thr Val Thr Thr Leu Ser Asp Leu Phe Asn Pro Asn Asn His Leu His Phe Pro Asn Tyr Leu Cys Asn Glu Gly Ile Met Cys Leu Val Leu Leu Thr Gly Pro His Trp Arg Ala Ser Leu Tyr Leu Trp Ile Ser Val Tyr Val Tyr Leu Ser Pro His Phe Leu Gln Leu Ser Tyr Gly Pro Phe Tyr Ser Ile Phe Ser Asp Asn Glu Gln Tyr Pro Tyr Leu Tyr Gln Met Gly Pro Lys Asp Ser Ser Leu Ala Leu Ala Met Val Ser Phe Ile Ile Tyr Phe Lys Trp Asn Trp Val Gly Leu Phe Ile Ser Asp Asp Asp Gln Gly Asn Gln Phe Leu Ser Glu Leu Lys Lys Glu Ser Gln Thr Lys Asp Ile Cys Phe Ala Phe Val Asn Met Ile Ser Val Ser Asp Val Ser Tyr Tyr His Lys Thr Glu Met Tyr Tyr Asn Gln Ile Val Met Ser Ser Thr Lys Val Ile Ile Ile Tyr Gly Glu Thr Asn Ser Ile Ile Glu Leu Ser Phe Arg Met Trp Ser Ser Pro Val Lys Gln Arg Ile Trp Val Thr Thr Lys Gln Phe Asp Cys Pro Thr Ser Lys Arg Asp Leu Thr His Gly Thr Phe Tyr Gly Thr Leu Thr Phe Leu His His Tyr Gly Glu Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Arg Tyr Asn Leu Arg Ser Thr Asp Leu Tyr Leu Val Met Pro Glu Trp Lys Tyr Phe Asn Tyr Glu Ala Ser Ala Ser Asn Cys Lys Ile Leu Arg Asn Tyr Leu Ser Asn Ile Ser Leu Glu Trp Leu Met Glu Gln Lys Phe Asp Met Ser Phe Ser Asp Tyr Ser His Asn Ile Tyr Asn Ala Val Tyr Ala Ile Ala His Ala Leu His Glu Lys Asn Leu Gln Glu Val Glu Asn Gln Ala Ile Asn Asn Ala Lys Gly Glu Asn Thr His Cys Leu Lys Leu Asn Ser Phe Leu Arg Lys Thr His Phe Thr Asn Ser Leu Gly Asn Arg Val Ile Met Lys Gln Arg Glu Val Val His Gly Asp Tyr Asn Ile Val His Met Trp Asn Phe Ser Gln Arg Leu Gly Ile Lys Val Lys Ile Gly Gln Phe Ser Pro His Phe Pro Gln Gly Gln Gln Leu His Leu Tyr Val Asp Met Thr Glu Leu Ala Thr Gly Ser Arg Lys Met Pro Ser Ser Val Cys Ser Ala Asp Cys His Pro Gly Phe Arg Arg Ile Trp Lys Glu Glu Met .

520 Ala Ala Cys Cys Phe Val Cys Asn Pro Cys Pro Glu Asn Glu Ile Ser 535 540 530 Asn Glu Thr Met Val Val Phe Trp Val Phe Val Lys His His Asp Thr 555 550 Pro Ile Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Leu Leu Ile Val 570 565 Ser Leu Met Phe Cys Phe Leu Cys Ser Phe Phe Phe Ile Gly Tyr Pro 590 585 580 Asn Arg Ala Thr Cys Ile Leu Gln Gln Ile Thr Phe Gly Ile Phe Phe 605 595 600 Thr Val Ala Ile Ser Thr Val Leu Ala Lys Thr Ile Thr Val Val Leu 615 620 Ala Phe Lys Val Thr Asp Pro Gly Arg Gln Leu Arg Ile Phe Leu Val 630 635 Ser Gly Thr Pro Asn Tyr Ile Ile Pro Ile Cys Ser Leu Leu Gln Cys 650 655 645 Ile Leu Cys Ala Ile Trp Leu Ala Val Ser Pro Pro Phe Val Asp Ile 665 670 Asp Glu His Ser Glu His Gly His Ile Ile Ile Val Cys Asn Lys Gly 675 685 Ser Ile Thr Ala Phe Tyr Cys Val Leu Gly Tyr Leu Ala Cys Leu Ala 695 700 Phe Gly Ser Phe Thr Ile Ala Phe Leu Ala Lys Asn Leu Pro Asp Thr 720 710 715 Phe Asn Glu Ala Lys Phe Leu Thr Phe Ser Met Leu Val Phe Cys Ala 730 725 Val Trp Val Thr Phe Leu Pro Val Tyr His Ser Thr Lys Gly Lys Val 745 740 Met Val Ala Val Glu Ile Phe Ser Ile Leu Ala Ser Ser Ala Gly Met 760 765 755 Leu Gly Cys Ile Phe Ala Pro Lys Val Tyr Ile Ile Leu Met Arg Pro 775 780 770 Asp Arg Asn Ser Ile His Lys Ile Arg Glu Lys Ser Tyr Phe 790

## (2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 3012 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence
  - (B) LOCATION: 3...2087
  - (D) OTHER INFORMATION: GOVN13B

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

AT GTC TAC CTG TCT CCA CAT TTC CTT CAG CTT TCC TAT GGA CCT TTC

Val Tyr Leu Ser Pro His Phe Leu Gln Leu Ser Tyr Gly Pro Phe

1 5 10 15

TAC TCC ATC TTC AGT GAT AAT GAA CAA TAT CCT TAT CTC TAT CAG ATG

Tyr Ser Ile Phe Ser Asp Asn Glu Gln Tyr Pro Tyr Leu Tyr Gln Met

20 25 30

GGC CCA AAG GAC TCA TCA CTA GCA TTG GCA ATG GTC TCC TTC ATA ATT

Gly Pro Lys Asp Ser Ser Leu Ala Leu Ala Met Val Ser Phe Ile Ile

35

40

45

WO 99/00422 PCT/US98/13680

				AAC Asn												191
				CTC Leu												239
				TTT Phe												287
				GAA Glu 100												335
				ATT Ile												383
-				TCA Ser												431
				TGC Cys												479
				CTT Leu												527
				GTA Val 180												575
				CCA Pro												623
				ATA Ile											GAA Glu	671
			Glu	CAG Gln	Lys	Phe		Met	Ser	Phe	Ser	Asp				719
				GCT Ala											AAA Lys 255	767
				TTT Phe 260											GAA Glu	815
				TTG Leu			_									863
				GGG Gly												911
CAT	· GGA	GAC	TAT	AAT	ATT	GTT	CAC	ATG	TGG	AAT	TTC	TCA	CAA	CGC	CTT	959

WO 99/00422 PCT/US98/13680

																•
His	Gly 305	Asp	Tyr	Asn	Ile	Val 310	His	Met	Trp	Asn	Phe 315	Ser	Gln	Arg	Leu	
	ATT Ile															1007
	CAG Gln															1055
	AAG Lys															1103
	AGA Arg															1151
	TGC Cys 385															1199
	AAT Asn															1247
	CAG Gln															1295
	CTT Leu															1343
	TGG Trp													_		1391
	AGA Arg 465														TTT Phe	1439
	TGC Cys															1487
	CAG Gln															1535
	CTG Leu															1583
	GGA Gly															1631
															TGG Trp	1679
															CAT His .	1727

WO 99/00422 PCT/US98/13680

- 165 -

560 565 570	575
GGC CAC ATC ATC ATT GTG TGC AAC AAG GGC TCC ATG His Ile Ile Val Cys Asn Lys Gly Ser Il	
TGT GTC CTG GGA TAC TTG GCC TGC CTG GCC TTT GG Cys Val Leu Gly Tyr Leu Ala Cys Leu Ala Phe Gl 595 600	
GCT TTC TTG GCA AAG AAC CTG CCT GAC ACA TTC AA Ala Phe Leu Ala Lys Asn Leu Pro Asp Thr Phe As 610 615	
TTG ACC TTC AGC ATG CTA GTG TTC TGC GCT GTC TG Leu Thr Phe Ser Met Leu Val Phe Cys Ala Val Tr 625 630 63	p Val Thr Phe Leu
CCT GTC TAC CAT AGC ACC AAG GGC AAG GTC ATG GT Pro Val Tyr His Ser Thr Lys Gly Lys Val Met Va 640 645 650	
TTC TCC ATC TTG GCA TCT AGT GCA GGG ATG CTG GG Phe Ser Ile Leu Ala Ser Ser Ala Gly Met Leu Gl 660 665	
CCC AAA GTT TAC ATC ATT TTA ATG AGA CCA GAC AG Pro Lys Val Tyr Ile Ile Leu Met Arg Pro Asp Ar 675	
AAA ATC AGG GAG AAA TCA TAT TTC TGAAAAGGTA TTT Lys Ile Arg Glu Lys Ser Tyr Phe 690 695	CAGGAAT TCTGTCAAAT 2117
GTAAAGTTGA TACATACACC CCAAATATTT AGTTACAGAG CA	TATATCTA GTTTTAGAAT 2177
CACTCTCACT GGTTCCTCTA GTTATGCATA GAAGTACCAT AT	
TTGTCTATAA AATCTTACAA TCATTCATTT GCTTAGTATC TT	
TCAAATAACT AGTACAATTT TATTCATTAT TTTGCTTTCA TO	
CTTCAAATAA ATTTTATAAG TCAGTTGAAT ATATAACCTT AC	· ·
GACAGACAGG GATTATACAT AGAAACAAAC TAACTAAAAA TO ACACATTTTC TTATTTCCAG TAGGAACACA TACTTGACAG AA	
TGCTCTTTAA GATATTGGCC AATAGTCTAA GCTGAAAATG T	
ACAAAAATAT TATATCCAAC AATGGACAGA ATCTGAGAAC TO	
ATAGTTGGAA GATACTGAGA AGGAGGTGA CCCATAGGAA TA	
CCTGGACAAC CAAGGTCCCT CAGACACTGA GCCACTAACA AC	
TATGAGGCCC CCAAAACATA TGCAACATAG GATTGCCTGG TO	
ACACACCTAA CCACAGAGAG ACTTCCCCAA GGGATTGGGG AC	
TGCGGATTGT CCCTTGATGA TTGGAAGGAG GTATTGGATG AC	
CTAGGAAGGG GATAATGATG GAACTGTAAA AAAAATTAAA AA	ададалала алала 3012

- (2) INFORMATION FOR SEQ ID NO:50:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 695 amino acids
  - (B) TYPE: amino acid (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOJECULE TYPE: protein
  (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Val Tyr Leu Ser Pro His Phe Leu Gln Leu Ser Tyr Gly Pro Phe Tyr 15 5

Ser Ile Phe Ser Asp Asn Glu Gln Tyr Pro Tyr Leu Tyr Gln Met Gly Pro Lys Asp Ser Ser Leu Ala Leu Ala Met Val Ser Phe Ile Ile Tyr Phe Lys Trp Asn Trp Val Gly Leu Phe Ile Ser Asp Asp Asp Gln Gly Asn Gln Phe Leu Ser Glu Leu Lys Lys Glu Ser Gln Thr Lys Asp Ile Cys Phe Ala Phe Val Asn Met Ile Ser Val Ser Asp Val Ser Tyr Tyr His Lys Thr Glu Met Tyr Tyr Asn Gln Ile Val Met Ser Ser Thr Lys Val Ile Ile Ile Tyr Gly Glu Thr Asn Ser Ile Ile Glu Leu Ser Phe Arg Met Trp Ser Ser Pro Val Lys Gln Arg Ile Trp Val Thr Thr Lys Gln Phe Asp Cys Pro Thr Ser Lys Arg Asp Leu Thr His Gly Thr Phe Tyr Gly Thr Leu Thr Phe Leu His His Tyr Gly Glu Ile Ser Gly Phe Lys Asn Phe Val Gln Thr Arg Tyr Asn Leu Arg Ser Thr Asp Leu Tyr Leu Val Met Pro Glu Trp Lys Tyr Phe Asn Tyr Glu Ala Ser Ala Ser Asn Cys Lys Ile Leu Arg Asn Tyr Leu Ser Asn Ile Ser Leu Glu Trp Leu Met Glu Gln Lys Phe Asp Met Ser Phe Ser Asp Tyr Ser His Asn Ile Tyr Asn Ala Val Tyr Ala Ile Ala His Ala Leu His Glu Lys Asp Leu Gln Glu Phe Glu Asn Gln Ala Ile Asn Asn Ala Lys Gly Glu Asn Thr His Cys Leu Lys Leu Asn Ser Phe Leu Arg Lys Thr His Phe Thr Asn Ser Leu Gly Asn Arg Val Ile Met Lys Gln Arg Glu Val Val His Gly Asp Tyr Asn Ile Val His Met Trp Asn Phe Ser Gln Arg Leu Gly Ile Lys Val Lys Ile Gly Gln Phe Ser Pro His Phe Pro Gln Gly Gln Gln Leu His Leu Tyr Val Asp Met Thr Glu Leu Ala Thr Gly Ser Arg Lys Met Pro Ser Ser Val Cys Ser Ala Asp Cys His Pro Gly Phe Arg Arg Ile Trp Lys Glu Glu Met Ala Ala Cys Cys Phe Val Cys Asn Pro Cys Pro Glu Asn Glu Ile Ser Asn Glu Thr Asn Met Asp Gln Cys Ala Asn Cys Pro Glu Tyr Gln Tyr Ala Asn Thr Glu Lys Asn Lys Cys Ile Gln Lys Gly Val Ile Val Leu Ser Tyr Glu Asp Pro Leu Gly Met Ala Leu Ala Leu Ile Ala Phe Cys Phe Ser Ala Phe Thr Val Val Val Phe Trp Val Phe Val Lys His His Asp Thr Pro Ile Val Lys Ala Asn Asn Arg Ile Leu Ser Tyr Leu Leu Ile Val Ser Leu Met Phe Cys Phe Leu Cys Ser Phe Phe Phe Ile Gly Tyr Pro Asn Arg Ala Thr Cys Ile Leu Gln Gln Ile Thr Phe Gly Ile Phe Phe Thr Val Ala Ile Ser Thr Val Leu Ala Lys Thr Ile Thr Val Val Leu Ala Phe Lys Val Thr Asp Pro Gly Arg Gln Leu Arg Ile Phe Leu Val Ser Gly Thr Pro Asn Tyr Ile .

540 530 535 Ile Pro Ile Cys Ser Leu Leu Gln Cys Ile Leu Cys Ala Ile Trp Leu 555 550 Ala Val Ser Pro Pro Phe Val Asp Ile Asp Glu His Ser Glu His Gly 565 570 575 His Ile Ile Ile Val Cys Asn Lys Gly Ser Ile Thr Ala Phe Tyr Cys 580 585 590 Val Leu Gly Tyr Leu Ala Cys Leu Ala Phe Gly Ser Phe Thr Ile Ala 595 600 605 Phe Leu Ala Lys Asn Leu Pro Asp Thr Phe Asn Glu Ala Lys Phe Leu 615 620 Thr Phe Ser Met Leu Val Phe Cys Ala Val Trp Val Thr Phe Leu Pro 630 635 Val Tyr His Ser Thr Lys Gly Lys Val Met Val Ala Val Glu Ile Phe 645 650 Ser Ile Leu Ala Ser Ser Ala Gly Met Leu Gly Cys Ile Phe Ala Pro 665 660 670 Lys Val Tyr Ile Ile Leu Met Arg Pro Asp Arg Asn Ser Ile His Lys 675 680 Ile Arg Glu Lys Ser Tyr Phe 690

#### (2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 435 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CAGACTCTGA	GCTACACCCT	CCTTGTCTCC	CTCACACTCT	GCTTTCTCTC	TTCCTCGCTC	60
TTCATCGGCC	GCCCCAGCCC	TGCCACCTGC	CTCCTCTCAC	AGACCACCTT	TGCAGCTGTG	120
TTCACAGTGG	CTGTGTTTTT	CTGCAGGGCC	TTCCAGGCTA	TAAGGCCAGA	AAGCAGGATC	180
CGAAAGTGGA	TGGGTCCCCA	AAAAACAAAT	TCTGTTGTCT	TCCTTTGCTC	CTTTACCCAA	240
GTGACCCTCT	GTGGAATCTG	GCTGGGGACA	GAGCCTCCCT	TCGTAAACAA	GGACCCTCAG	300
TTCATGCCTG	GCTACATCAT	TATCCAGTGT	AATGAGGGCT	CCGTCACTGC	CTTCTACTCT	360
GTCTTGGGCT	ACTTGGGCTT	CTTGGTTTTA	GGGTCCCTTG	CTGTAGCCTT	TCTGGCAAGG	420
AACCTGCCTG	ATGCT					435

## (2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 145 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Gln Thr Leu Ser Tyr Thr Leu Leu Val Ser Leu Thr Leu Cys Phe Leu 1 10 Ser Ser Ser Leu Phe Ile Gly Arg Pro Ser Pro Ala Thr Cys Leu Leu 20 25 30 Ser Gln Thr Thr Phe Ala Ala Val Phe Thr Val Ala Val Phe Phe Cys 35 40 Arg Ala Phe Gln Ala Ile Arg Pro Glu Ser Arg Ile Arg Lys Trp Met 55 60 Gly Pro Gln Lys Thr Asn Ser Val Val Phe Leu Cys Ser Phe Thr Gln 70 75 80 . 

 Val
 Thr
 Leu
 Cys
 Gly
 Ile
 Trp
 Leu
 Gly
 Thr
 Glu
 Pro
 Pro
 Pro
 Pro
 95

 Lys
 Asp
 Pro
 Gln
 Phe
 Met
 Pro
 Gly
 Tyr
 Ile
 Ile
 Ile
 Gln
 Cys
 Asn
 Glu

 Gly
 Ser
 Val
 Thr
 Ala
 Phe
 Tyr
 Ser
 Val
 Leu
 Gly
 Tyr
 Leu
 Gly
 Phe
 Leu

 Val
 Leu
 Gly
 Ser
 Leu
 Ala
 Val
 Ala
 Phe
 Leu
 Ala
 Arg
 Asn
 Leu
 Pro
 Asp

 Ala
 145
 Ile
 Il

### (2) INFORMATION FOR SEQ ID NO:53:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 474 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CCCATTGTGA AGGCTAATAA CCAGACTCTG AGCTACACCC TCCTTGTCTC CCTCACACTC
TGCTTTCTCT CTTCCTCGCT CTTCATCGGC CGCCCCAGCC CTGCCACCTG CCTCCTCTCA 120
CAGACCACCT TTGCAGCTGT GTTCACAGTG GCTGTGTTTT CTGCAGGGCC TTCCAGGCTA 180
TAAGGCCAGA AAGCAGGATC CGAAAGTGGA TGGGTCCCCA AAAAACAAAT TCTGTTGTCT 240
TCCTTTGCTC CTTTACCCAA GTGACCCTCT GTGGAATCTG GCTGGGGACA GAGCCTCCCT 300
TCGTAAACAA GGACCCTCAG TTCATGCCTG GCTACATCAT TATCCAGTGT AATGAGGGCT 360
CCGTCACTGC CTTCTACTCT GTCTTGGGCT ACTTGGGCTT CTTGGTTTTA GGGTCCCTTG 420
CTGTAGCCTT TCTGGCAAGG AACCCGCCAG ATACGTTCAA TGAGGCCAAG TTAA 474

## (2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 338 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

ACTCCCATTG	TGAAGGCCAA	CAACTGCCAG	CTCAGCTATC	TCCTGCTGTC	CTCCTTGGCC	60
CTCAGCTTCC	TCTGCCCCTT	CATGTTCATT	GGCCACCCAG	ACCCCATCAC	TTGTGCTGTG	120
CACNAGGCAG	ATTTTGGGGT	CACCTTCATG	GTCTGCACAT	CCACTGTGCT	GGCCAAGACC	180
ATCGTGGTGG	TGGCAGCCTT	CCATGCCACC	CAGGCAGACA	CTCAGCTTAG	GGGGTGGGCG	240
GGGACAGTCC	TCCTCAGCAC	CATCCTCACT	GTTCCCTGAC	CCAGGCAGCC	TTGTGTGCAC	300
TCTGGGTGAC	CAGATGGCCC	CCTCAGCCTG	TAAAATCT			338

#### (2) INFORMATION FOR SEQ ID NO:55:

- (i) SEOUENCE CHARACTERISTICS:
  - (A) LENGTH: 182 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AACCTNCCCG	ATACNTTCAA	TGAAGCCAAG	TTCTTGATGT	TCAGCATGCT	GATGTTATGT	60
ACTGTTTGAA	TTACCTTCCA	TACTGTGTAA	CATAGCACCA	AAGGGAAGGT	CATGGTTGCC	120
TTGGAAATAT	TCTCCACCTT	GACTTCCAGT	GCTGAGTGCT	AGGNTGTATC	TTCGCNCCAA	180

PCT/US98/13680

- 169 -

AA . 182

- (2) INFORMATION FOR SEQ ID NO:56:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 37 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

### ATTGGATCCA GGCCGCTCTG GACAAAATAT GAATTCT

37

- (2) INFORMATION FOR SEQ ID NO:57:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 37 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

### GGCACATGGA CGAAATCTTG GTACTCTTCA GAATTCT

37

- (2) INFORMATION FOR SEQ ID NO:58:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 51 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

- (2) INFORMATION FOR SEQ ID NO:59:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1079 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Met Ala Ser Tyr Ser Cys Cys Leu Ala Leu Leu Ala Leu Ala Trp His 1 5 10 15 Ser Ser Ala Tyr Gly Pro Asp Gln Arg Ala Gln Lys Lys Gly Asp Ile.

Ile Leu Gly Gly Leu Phe Pro Ile His Phe Gly Val Ala Ala Lys Asp Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu Cys Ile Arg Tyr Asn Phe Arg Gly Phe Arg Trp Leu Gln Ala Met Ile Phe Ala Ile Glu Glu Ile Asn Ser Ser Pro Ser Leu Leu Pro Asn Met Thr Leu Gly Tyr Arg Ile Phe Asp Thr Cys Asn Thr Val Ser Lys Ala Leu Glu Ala Thr Leu Ser Phe Val Ala Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe Cys Asn Cys Ser Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala Thr Gly Ser Gly Val Ser Thr Ala Val Ala Asn Leu Leu Gly Leu Phe Tyr Ile Pro Gln Val Ser Tyr Ala Ser Ser Ser Arg Leu Leu Ser Asn Lys Asn Gln Tyr Lys Ser Phe Leu Arg Thr Ile Pro Asn Asp Glu His Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr Phe Arg Trp Asn Trp Val Gly Thr Ile Ala Ala Asp Asp Asp Tyr Gly Arg Pro Gly Ile Glu Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe Ser Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile Gln Gln Val Val Glu Val Ile Gln Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser Gly Pro Asp Leu Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile Thr Gly Arg Ile Trp Leu Ala Ser Glu Ala Trp Ala Ser Ser Leu Ile Ala Met Pro Glu Tyr Phe His Val Val Gly Gly Thr Ile Gly Phe Gly Leu Lys Ala Gly Gln Ile Pro Gly Phe Arg Glu Phe Leu Gln Lys Val His Pro Arg Lys Ser Val His Asn Gly Phe Ala Lys Glu Phe Trp Glu Glu Thr Phe Asn Cys His Leu Gln Glu Gly Ala Lys Gly Pro Leu Pro Val Asp Thr Phe Val Arg Ser His Glu Glu Gly Gly Asn Arg Leu Leu Asn Ser Ser Thr Ala Phe Arg Pro Leu Cys Thr Gly Asp Glu Asn Ile Asn Ser Val Glu Thr Pro Tyr Met Asp Tyr Glu His Leu Arg Ile Ser Tyr Asn Val Tyr Leu Ala Val Tyr Ser Ile Ala His Ala Leu Gln Asp Ile Tyr Thr Cys Leu Pro Gly Arg Gly Leu Phe Thr Asn Gly Ser Cys Ala Asp Ile Lys Lys Val Glu Ala Trp Gln Val Leu Lys His Leu Arg His Leu Asn Phe Thr Asn Asn Met Gly Glu Gln Val Thr Phe Asp Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile Ile Asn Trp His Leu Ser Pro Glu Asp Gly Ser Ile Val Phe Lys Glu Val Gly Tyr Tyr Asn Val Tyr Ala Lys Lys Gly Glu Arg Leu Phe Ile Asn Glu Glu Lys Ile Leu Trp Ser Gly Phe Ser Arg Glu Val Pro Phe Ser Asn Cys Ser Arg 

Asp Cys Gln Ala Gly Thr Arg Lys Gly Ile Ile Glu Gly Glu Pro Thr Cys Cys Phe Glu Cys Val Glu Cys Pro Asp Gly Glu Tyr Ser Gly Glu Thr Asp Ala Ser Ala Cys Asp Lys Cys Pro Asp Asp Phe Trp Ser Asn Glu Asn His Thr Ser Cys Ile Ala Lys Glu Ile Glu Phe Leu Ala Trp Thr Glu Pro Phe Gly Ile Ala Leu Thr Leu Phe Ala Val Leu Gly Ile Phe Leu Thr Ala Phe Val Leu Gly Val Phe Ile Lys Phe Arg Asn Thr Pro Ile Val Lys Ala Thr Asn Arg Glu Leu Ser Tyr Leu Leu Phe Ser Leu Leu Cys Cys Phe Ser Ser Ser Leu Phe Phe Ile Gly Glu Pro Gln Asp Trp Thr Cys Arg Leu Arg Gln Pro Ala Phe Gly Ile Ser Phe Val Leu Cys Ile Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu Val Phe Glu Ala Lys Ile Pro Thr Ser Phe His Arg Lys Trp Trp Gly Leu Asn Leu Gln Phe Leu Leu Val Phe Leu Cys Thr Phe Met Gln Ile Leu Ile Cys Ile Ile Trp Leu Tyr Thr Ala Pro Pro Ser Ser Tyr Arg Asn His Glu Leu Glu Asp Glu Ile Ile Phe Ile Thr Cys His Glu Gly Ser Leu Met Ala Leu Gly Ser Leu Ile Gly Tyr Thr Cys Leu Leu Ala Ala Ile Cys Phe Phe Phe Ala Phe Lys Ser Arg Lys Leu Pro Glu Asn Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu Ile Phe Phe Ile Val Trp Ile Ser Phe Ile Pro Ala Tyr Ala Ser Thr Tyr Gly Lys Phe Val Ser Ala Val Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu Leu Ala Cys Ile Phe Phe Asn Lys Val Tyr Ile Ile Leu Phe Lys Pro Ser Arg Asn Thr Ile Glu Glu Val Arg Ser Ser Thr Ala Ala His Ala Phe Lys Val Ala Ala Arg Ala Thr Leu Arg Arg Pro Asn Ile Ser Arg Lys Arg Ser Ser Ser Leu Gly Gly Ser Thr Gly Ser Ile Pro Ser Ser Ser Ile Ser Ser Lys Ser Asn Ser Glu Asp Arg Phe Pro Gln Pro Glu Arg Gln Lys Gln Gln Gln Pro Leu Ser Leu Thr Gln Gln Gln Gln Gln Gln Gln Pro Leu Thr Leu His Pro Gln Gln Gln Gln Pro Gln Gln Pro Arg Cys Lys Gln Lys Val Ile Phe Gly Ser Gly Thr Val Thr Phe Ser Leu Ser Phe Asp Glu Pro Gln Lys Asn Ala Met Ala His Arg Asn Ser Met Arg Gln Asn Ser Leu Glu Ala Gln Arg Ser Asn Asp Thr Leu Gly Arg His Gln Ala Leu Leu Pro Leu Gln Cys Ala Asp Ala Asp Ser Glu Met Thr Ile Gln Glu Thr Gly Leu Gln Gly Pro Met Val Gly Asp His Gln Pro Glu Met Glu Ser Ser Asp Glu Met Ser Pro Ala Leu Val Met Ser Thr Ser Arg Ser Phe Val Ile Ser Gly Gly Gly Ser Ser Val

PCT/US98/13680

26

1065 1070 1060 Thr Glu Asn Val Leu His Ser 1075

- (2) INFORMATION FOR SEQ ID NO:60:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ix) FEATURE:
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 3...3
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 12...12
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 15...15
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 18...18
  - (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

## BTNYAYCARR TNGCNMCNAA RGAYAC

(2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ix) FEATURE:
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 6...6
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 9...9
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 12...12
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 18...18

PCT/US98/13680

- 173 -	-
(D) OTHER INFORMATION: Inosine	
(A) NAME/KEY: Modified Base (B) LOCATION: 2121	
(D) OTHER INFORMATION: Inosine	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:	
GYRTKNGCNR YNRCRTRNAC NRCRTT	26
(2) INFORMATION FOR SEQ ID NO:62:	
<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 26 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
(ix) FEATURE:	
<ul><li>(A) NAME/KEY: Modified Base</li><li>(B) LOCATION: 33</li></ul>	
(D) OTHER INFORMATION: Inosine	
(A) NAME/KEY: Modified Base (B) LOCATION: 99	
(D) OTHER INFORMATION: Inosine	
(A) NAME/KEY: Modified Base (B) LOCATION: 1212	
(D) OTHER INFORMATION: Inosine	
(A) NAME/KEY: Modified Base (B) LOCATION: 1313	
(D) OTHER INFORMATION: Inosine	
(A) NAME/KEY: Modified Base (B) LOCATION: 2424	
(D) OTHER INFORMATION: Inosine	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:	
MRNTGYCCNK ANNAYMARTA YGCNAA	26
(2) INFORMATION FOR SEQ ID NO:63:	
<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li></ul>	
(B) TYPE: nucleic acid	
(C) STRANDEDNESS: single (D) TOPOLOGY: linear	

(ix) FEATURE:

(A) NAME/KEY: Modified Base (B) LOCATION: 2...2 (D) OTHER INFORMATION: Inosine

WO 99/00422 PCT/US98/13680

- 174 -

- (A) NAME/KEY: Modified Base
- (B) LOCATION: 5...5
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 8...8
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 11...11
  (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base (B) LOCATION: 14...14
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 20...20
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 26...26
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 29...29
- (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

31

## GNCKNAYNAR NATNAYRTAN MWYTTNGGNA C

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (ix) FEATURE:

- (A) NAME/KEY: Modified Base
- (B) LOCATION: 3...3
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 6...6
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 9...9
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base(B) LOCATION: 12...12

PCT/US98/13680

- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 16...16
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 24...24
- (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

### ATNWSNYTNR TNTTYNGYTT YYTNTG

26

- (2) INFORMATION FOR SEQ ID NO:65:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid

  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ix) FEATURE:
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 2...2
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 5...5
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 11...11
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 17...17
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 20...20
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 23...23
  - (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

## RNATNSWRAA NAYYTCNACN RCNACCAT

28

- (2) INFORMATION FOR SEQ ID NO:66:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs

- (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ix) FEATURE: (A) NAME/KEY: Modified Base
- - (B) LOCATION: 6...6
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 9...9
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base (B) LOCATION: 12...12

  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 15...15
  - (D) OTHER INFORMATION: Inosine
  - (A) NAME/KEY: Modified Base
  - (B) LOCATION: 21...21
  - (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

## GAYACNCCNA TNGTNAARGC NAAYAA

26

- (2) INFORMATION FOR SEQ ID NO:67:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

## (ix) FEATURE:

- (A) NAME/KEY: Modified Base
- (B) LOCATION: 3...3
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 6...6
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 12...12
- (D) OTHER INFORMATION: Inosine
- (A) NAME/KEY: Modified Base
- (B) LOCATION: 15...15
- (D) OTHER INFORMATION: Inosine

- 177 -

- (A) NAME/KEY: Modified Base
- (B) LOCATION: 24...24
- (D) OTHER INFORMATION: Inosine
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

#### AANGTNAYCC ANACNSWRCA RAANAC

26

- (2) INFORMATION FOR SEO ID NO:68:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2550 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

ATGAAGCAGC TCTGCGCTTT CACTATTTCT TTGTTGTTTC TGAAGTTTTC TCTCATCCTG TGCTGTTTGA CTGAACCAAG TTGCTTTTGG AGAATAAGGA ATAGTGAAGA TAGTGATGGA 120 GATTTACAAA GGGAATGTCA TTTTTACCTT TGGAAAACTG ATGAACCTAT TGAAGATAGT 180 TTTTATAATT ATGATTTAAG TTTTAGAATT GCAGCAAGTG AATATGAGTT TCTTCTCGTA ATGTTTTTTG CTATCGATGA GATCAACAGG AATCCTTATC TTTTACCCAA CATAACTTTG 240 300 ATGTTCTCCT TCATTGGTGG AAACTGTCAG GATTTATTGA GAGTTATGGA CCAAGCATAT 360 ACACAAATAA ATGGACATAT GAATTTTGTT AATTATTTCT GTTATTTAGA TGATTCATGT 420 GCCATAGGTC TTACAGGACC ATCATGGAAA ACTTCCTTAA AACTGGCAAT GCACTCTTCG 480 ATGCCACTGG TTTTCTTTGG ACCATTTAAT CCTAACCTAC GCGACCATGA CCGGCTGCCC 540 CATGTCCATC AGGTAGCCCC CAAGGACACA CATTTGTCCC ATGGCATGGT CTCCTTGATG 600 TTTCACTTTA GATGGACTTG GATAGGACTG GTCATCTCAG ATGATGACCA GGGTATTCAG TTTCTCTCAG ATTTAAGAGA AGAAAGCCAA AGGCATGGGA TCTGTTTAGC TTTTGTTAAT 720 ATGATCCCAG AAAACATGCA GATATACATG ACAAGGGCTA CAATATATGA TAAACACATT 780 ATGACATCTT CAGCAAAGGT TGTTATCATT TATGGTGAAA TGAACTCTAC TCTAGAAGCA 840 AGCTTTAGAA GATGGGAAGA GTTAGGTGCT CGGAGAATCT GGATCACAAC CTCACAATGG GATGTCATCA CAAATAAAAA AGACTTCACC CTTAATCTCT TCCATGGGAT CATCACTTTT 960 GAACATCATA GATTTGAGAT TCCTAAATTA AATAATTCA TGCAACCAAT GAACACTGCC AAATACCCAG TAGATATTTC TCATACTATA TTGGAGTGGA ATTATTTTAA TTGTTCAATA 1020 1080 TCTAAGAACA GCATTAGAAT GCATCATATT ACATTCAACA ACACCTTGGA ATGGACATCA CTGCACAACT ATGATGTGGC GATGAGTGAT GAAGGTTACA ATTTGTACAA TGCTGTTTAT 1200 GCTGTGGCCC ACACCTACCA TGAATACATT TTTCAACAAG TAGAGTCTCA GAAAAAGGCA AAACCCAAAA GATATTTCAC TGCTTGTCAG CAGGTGTCTT CCTTGATGAA AACCAGGGTA 1260 TTTACGAACC CTGTTGGAGA ACTGGTGAAC ATGAAGCATA GGGAAAATCA GTGTACAGAG 1380 TATGATATTT TCATCATTTG GAATTTTCCA CAAGGCCTTG GATTAAAAGT GAAAATAGGA AGCTATTTAC CTTGTTTTCC ACAGAGACAA AAACTTCATA TATCTGATGA TTTGGAATGG 1500 GCCAAGGGAG GAACATCACC TCAGGTTCCC TCCTCCGTGT GTAGTGTGGC ATGTACTGCT GGATTCAGGA AAATTTATCA AAAAGAAACA GCAGACTGCT GCTTTGATTG TGTTCAGTGC 1620 CCAGAAAATG AGATTTCCAA CGAAACAGAT ATGGAACAGT GTGTGAGGTG TCCAGATGAT AAGTATGCCA ACATAGAGCA AACCCACTGC CTCTCAAGAG CTGTATCATT TCTGGCTTAT GAAGATTCAT TGGGGATGGC TCTAGGCTGC ATGGCACTGT CCTTCTCAGC CATCACAATT CTAATCCTCG TCACATTTGT GAAGTACAAA GATACTCCCA CTGTGAAGGC CAATAACCGC 1860 ATTCTCAGCT ACATCCTGCT CATCTCTCTC GTCTTCTGCT TTCTCTGCTC CCTGCTCTTC 1920 ATTGGACCTC CCGACCAGGT CACCTGCATC TTTCAGCAGA CCACATTTGG AGTATTGTTC 1980 ACTGTGTCTG TTTCTACAGT GTTGGCCAAA ACAATAACTG TGGTCATGGC TTTCAAGCTC 2040 ACTACTCCAG GAAGAAGGAT GAGAGGGATG ATGATGACAG GGGCACCTAA GTTGGTCATT CCCATTTGTA CCCTGATCCA ACTTGTTCTC TGTGGAATCT GGTTGGTCAC ATCTCCTCCC 2160 TTTATTGACA GAGACATACA ATCTGAGCAT GGGAAGATTG TCATTCTTTG CAATAAAGGC TCAGTCATTG CCTTCCACGT CGTCCTGGGA TACTTGGGCT CCTTGGCTCT GGGGAGCTTC 2280 ACGTTGGCTT TCCTGGCTAG GAACCTTCCT GACACATTCA ATGAAGCCAA GTTCCTAACT TTCAGCATGC TGGTGTTCTG CAGTGTCTGG ATCACCTTCC TCCCTGTCTA CCACAGCACC 2340 2400 AGGGGGAGGG TCATGGTGGT TGTGGAGGTT TTCTCCATCT TGGCTTCTAG TGCAGGGTTG 2460 CTAATGTGTA TCTTTGTCCC AAAGTGTTAT GTTATTTTAA TTAGACCAGA TTCAAATTTT 2520 ATAAAGAACC ACAAAGGTAA ATTGCTTTAT 2550

# (2) INFORMATION FOR SEQ ID NO:69:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2424 base pairs (B) TYPE: nucleic acid

  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

ATGAAGCAGC	TCTGCACTTT	CACTATTTCA	TTGTTGTTTC	TGAAGTTTTC	TCTCATCTTG	60
TGCTGTTGGA	GTGAACCAAG	CTGCTTTTGG	AGGATAAAGA	AGAGTGAAGA	TAATGATGGA	120
GATTTACAAA	GGGAGTGTCA	TTTTTACCTT	TGGAAAACTG	ATGAACCTAT	TGAAGATAGT	180
TTTTATAATT	ATGATTTAAG	TTTTAGAATT	GCAGGAAGTG	AATATGAGCT	TCTTCTGGTA	240
ATGTTTTTTG	CTACTGATGA	GATCAACAAG	AATCCTTATC	TTTTACCCAA	CATGAGTTTG	300
ATGTTCTCCA	TCATTGGTGG	AAACTGTCAT	GATTTATTGA	GAAGTCTGGA	TCAAGAATAT	360
GCACAAATAG	ATGGACATAT	GAATTTTGTT	AATTATTTCT	GTTATTTAGA	TGATTCATGT	420
GCCACAGGCC	TTACAGGACC	ATCATGGAAA	ACATCCTTAA	AACTGGCAAT	GCATTCTTCA	480
ATGCCACTGG	TTTTCTTTGG	ACCATTTAAT	CCTAACCTAC	GCGACCATGA	CCGGCTGCCC	540
CATGTCCATC	AGGTAGCCCC	CAAGGACACA	CATTTGTCCC	ATGGCATGGT	CTCCTTGATG	600
TTTCATTTTA	GGTGGACTTG	GATAGGACTG	GTCATCTCAG	ATGATGATCA	GGGTATTCAG	660
TTTCTCTCAG	ATTTAAGAGA	AGAAAGCCAA	AGGCATGGGA	TCTGTTTGGC	TTTTGTTAAT	720
ATGATCCCAG	AAAACATGCA	GATATACATG	ACAAGGGCTA	CAATATATGA	TACACAAATT	780
ATGACATCTT	CAGCAAAGGT	TGTTATCATT	TATGGTGACA	TGAACTCTAC	TCTAGAAGCA	840
AGCTTTAGAA	GATGGGAAGA	GTTAGGTGCT	CGGAGAATCT	GGATCACAAC	CACACAATGG	900
GATGTCATCA	CAAATAAAAA	AGACTTCACC	CTTAATCTCT	TCCATGGGAC	TATTACTTTT	960
GCACACCACA	AAGATGAGAT	TCCTAAATTT	AGGAATTTTA	TGCAAACAAA	GAAAACTGCC	1020
AAATACCTTG	TAGATATTTC	TCATACTATT	TTGGAGTGGA	ATTATTTTAA	TTGTTCAATC	1080
TCTAAGAACA	GCAGTAAAAT	GGGTCATTTT	ACATTCAACA	ACACATTGCA	ATGGACAGCA	1140
CTGCACAACT	ATGATATGGC	CCTGAGCGAT	GAAGGTTACA	ATTTGTATAA	TGCTGTTTAT	1200
GCTGTGGCCC	ACACCTACCA	TGAATACATT	CTTCAACAAG	TAGAGTCTCA	GAAAAAGGCA	1260
AAACCCAAAA	GATATTTCAC	TGCTTGTCAG	CAGGTGTCTT	CCTTGATGAA	AACCAGGGTA	1320
TTTATGAACC	CTGTTGGAGA	ACTGGTGAAC	ATGAAGCATA	GGGAAAATCA	GTGTACAGAG	1380
TATGATATTT	TCATCATTTG	GAATTTTCCA	CAAGGCCTTG	GATTAAAAGT	GAAAGTAGGA	1440
AGCTATTTAC	CTTGCTTTCC	AAAGAGTCAA	CAACTTCATA	TAGCTGATGA	TTTGGAATGG	1500
GCCATGGGAG	GAACATCAGT	GGATATGGAA	CAGTGTGTGA	GATGTCCAGA	TATAAATAT	1560
GCCAATTTAG	AGCAAACCCA	CTGCCTCCAA	AGAACGGTGT		TTATGAAGAT	1620
CCATTGGGGA	TGGCTCTAGG	CTGCATGGCA	CTGTCCTTCT	CGGCCATCAC	AATTCTAGTC	1680
CTCGTCACAT	TTGTGAAGTA	CAAGGATACT	CCCATTGTGA	AGGCCAATAA	CCGCATTCTC	1740
AGCTACATCC	TGCTCATCTC	TCTCGTCTTC	TGCTTTCTCT		CTTCATTGGA	1800
	AGGTCACCTG				GTTCACTGTG	1860
TCTGTTTCTA	CAGTGTTGGC	CAAAACAATA	ACTGTGGTCA	TGGCTTTCAA	GCTCACTACT	1920
CCAGGAAGAA	GGATGAGAGG	GATGATGATG	ACAGGGGCAC	CTAAGTTGGT	CATTCCCATT	1980
TGTACCCTGA	TCCAACTTGT	TCTCTGTGGA	ATCTGGTTGG	TCACATCTCC	TCCCTTTATT	2040
	TACAATCTGA			TTTGCAATAA		2100
GTTGCCTTCC	ACGTCGTCCT					2160
GCTTTCTTGG	CTAGGAACCT	TCCTGACACA	TTCAATGAAG	CCAAGTTCCT	AACTTTCAGC	2220
ATGCTGGTGT				TCTACCACAG		2280
AAGGTCATGG	TGGTTGTGGA					2340
TGTATCTTTG		TTATGTTATT	TTAATTAGAC	CAGATTCAAA	TTTTATACAG	2400
AACCACAAAG	GTAAATTGCT	TTAT				2424

- (2) INFORMATION FOR SEQ ID NO:70:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2409 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

CATTTTTACC TTGG	EGGCAGT TGATAAACC	A ATTGAAGATA	ATTTTTATAA	TTCACTTTTA	60
AAGTTTAGAA TTGC	LAGCAAG TGAATATGA	3 TTTCTTCTGG	TAATGTTTTT	TGCTACTGAT	120
GAGATCAACA AGAA	ATCCTTA TCTTTTACC	C AACATAACTT	TGATGTTCTC	CATCATTGGT	180
GGAAACTGTC ATGA	ATTTATT GAGAGGTTT	G GATCAAGCAT	ATACACAAAT	AAATGGACAT	240
ATGAATTTTG TTAA	ATTATTT CTGTTATTT.	A GATGATTCAT	GTGCCATAGG	TCTTACAGGA	300
CCATCATGGA AAAC	CATCCTT AAATCTGGC	A ATGCATTCTT	CAATGCCACT	GGTTTTCTTT	360
GGATCATTTA ATCC	CTAACCT ACATGACCA	r GACCGGCTGC	ACCATGTCCA	TCAAGTAGCC	420
ACCAAGGACA CACA	ATTTGTC CCATGGCAT	r gtctccttga	TGTTTCATTT	TAGATGGACT	480
TGGATAGGAC TGGT	CATCTC AGATGATGA	C AAGGGTATTC	AGTTTCTCTC	AGATTTAAGA	540
GAAGAAAGCC AAAG	GCATGG GATCTGTTT.	A GCTTTTGTTA	ATATGATCCC	AGAAAACATG	600
CAGATATACA TGAC	CAAGGGC TACAATATA	r gataaacaaa	TTATGACGTC	TTTAGCAAAA	660
GTTGTTATCA TTTA	ATGGTGA AATGAACTC	r acactagaag	TAAGCTTTAG	AAGATGGGAA	720
AATTTAGGTG CTCG	GAGAAT CTGGATCAC	A ACCTCACAAT	GGGATGTCAT	CACAAATAAA	780
AAAGAATTCA CCCT	TAATCT CTTCCATGG	ACTATTACTT	TTGCACACCG	CAGATTTGAG	840
ATTCCTAAAT TTAA	VAAAATT TATGCAAAC.	A ATGAACACTG	CCAAATACCC	AGTAGATATT	900
TCTCATACTA TATT	rggagtg gaattattt	r aattgttcaa	TCTCTAAGAA	CAGCAGTAAA	960
ATGGATCATA TTAC	CATTCAA CAACACATT	G GAATGGACAG	CACTGCACAA	CTATGATATG	1020
GTGATGAGTG ATGA	AAGGTTA CAATTTGTA	F AATGCTGTTT	ATGCTGTGGC	CCACACCTAC	1080
CATGAACATA TTTT	TTCAACA AGTAGAGTC	r cagaaaaagg	CAAAACCCAA	AAGATTTTTC	1140
ACTGTTTGTC AGCA	AGGTGTC TTCCTTGAT	<b>AAAACCAGGG</b>	TATTTACTAA	CCCTGTTGGA	1200
GAACTGGTGA ACAT	rgaagca tagggaaaa	r cagtgtacag	AGTATGACAT	TTTCCTCATT	1260
TGGAACTTTC CACA	AAGGCCT TGGATTAAA	A GTGAAAATAG	GAAGCTATTT	ACCTTGTTTT	1320
CCACAGAGAC AAGA	AACTTCA TATATCTGA	r gatttggaat	GGGCCATGGG	AGGAACATCA	1380
GTGGTTCCCT CCTC	CTGTGTG TAGTGTGGC	A TGTACTGCAG	GATTCAGGAA	AATTCATCAG	1440
AAAGAAACAG CAGA	ACTGCTG CTTTGATTG	r gttcagtgcc	CAGAAAATGA	GGTTTCCAAT	1500
GAAACAGATA TGGA	ACAGTG TGTGAAGTG	r ccatatgata	AGTATGCCAA	CATAGAGAAA	1560
ACCCACTGCC TCTC	CAAGAGC TGTATCATT	r ctggcttatg	AAGATCCATT	GGGGATAGCT	1620
CTAGGCTGCA TAGC	CACTGTC CTTCTCAGC	C ATCACAATTC	TAGTACTAAT	CACATTTTTG	1680
	CTCCCAT TGTGAAGGC		TTCTCAGCTA	CATCCTGCTC	1740
ATCTCTCTAG TCTT	CTGCTT TCTCTGCTC			AAACCAGGTC	1800
TCCTGCGTCT TGCA	AGCAGAC CACATTTGG	A GTATTTTCA	CTGTGTCTGT	TTCTACAGTG	1860
TTGGCCAAAA CAAT	PAACTGT GGTCATGGC	r ttcaagctca	CTACTCCAGG	AAGAAGAATG	1920
AGAGAGATGT TGGT	raacagg ggcacctaa	G TTGGTCATTC	CCATTTGTAC	CCTAATCCAA	1980
	SAATCTG GTTGATAAC		TTATTĢACAG	AGATATACAA	2040
TCTGAGCATG GGAA	AGATTGT CATTCTTTG	C AATAAAGGCT	CTGTCATTGC	CTTCCATGTT	2100
GTCCTGGGAT ACTI	RGGGCTC CTTGGCTCT	G GGGAGCTTCA	CTTTGGCTTT	CTTGGCTAGG	2160
AACCTTCCTG ACAC	CATTCAA TGAAGCCAA			GGTGTTCTGC	2220
	CCTTTCT CCCTGTCTA		GGGGGAAGGT	CATGGTGGTT	2280
	CAATCTT GGCTTCTAG		TAATGTGTAT		2340
	TTTTAGT TAGACCAGA	I TCAAATTTTA	TACGGAAGTA	CAAAGATAAA	2400
TTTCGTTAT			•		2409

## (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2556 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single

- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

ATGTTCATTT	TCATGGGAGT	CTTCTTCCTA	CTTAATATTA	CACTTCTCAT	GGCCAATTTC	60
ATTGATCCCA	GGTGCTTTTG	GAGAATAAAT	TTGGATGAAA	TAACGGATGA	ATATTTGGGA	120
TTATCTTGTG	CTTTCATCCT	GGCAGCTGTT	CAGACACCCA	TTGAAAAAGA	TTATTTCAAC	180
ACGACTCTTA	ATTTTCTAAA	AACTACTAAA	AACCACAAAT	ATGCTTTGGC	ATTGGTGTTT	240
GCAATGGATG	AAATCAACAG	ATATCCTGAT	CTTTTACCAA	ATATGTCTTT	GATTATCAGA	300
TACTCTTTGG	GCCATTGTGA	TGGAAAAACT	GTAACACCTA	CACCATATTT	ATTTCATAGA	360
AAAAAGCAAA	GCCCTATTCC	TAATTATTTC	TGTAATGAAG	AGAGTATGTG	TTCATTTCTG	420
CTTTCAGGAC	CCAATTGGGA	TGAATCTTTA	AGTTTCTGGA	<b>AGTACCTGGA</b>	CAGCTTCTTA	480
TCTCCACGTA	TCCTTCAGCT	TTCCTATGGA	TCTTTCAGTT	CCATCTTCAG	TGATGATGAA	540
CAATATCCCT	ATCTCTATCA	GATGGCCCCA	AAAGACACAT	CTCTAGCATT	GGCAATGGTC	600
TCCTTCATAC	TTTATTTGAA	ATGGAATTGG	ATTGGCCTTG	TCATCCCAGA	TGATGATCAA	660

- 180 -

GGAAACCAAT	TTCTTTTAGA	GTTGDAGAAA	CAGAGTGAAA	ACABAGABAT	TTGCTTTGCC	720
TTTGTGAAAA		TGATGAAGTT		AAAAAACTGA		780
AAACAAATTG	TGAAGTCACT	AACAAATGTT		ATGGAGAAAC	ATATAATTTC	840
ATTGATTTGA	TCTTCAGAAT	GTGGGAACCT	CCCATTTTAC	AGAGAATATG	GATCACCACA	900
AAACAATTGA	ATTTCCCTAC	CAGTAAGACA	GACATAAGTC	ATGACACATT	CTATGGATCA	960
CTTACTTTTC	TACCCCACCA	TGGTGAGATT	TCTGGCTTTA	AAAATTTTGT	ACAGACATGG	1020
TTCCATCTCA	GAAACACAGA	TTTATGTCTA	GTAATGCCAG	AGTGGAAATA	TATTAACTCT	1080
GAAGACTCAG	CATCTAATTG	TAAAATACTT	AAGAACAGTT	CATCTGATGC	CTCATTTGAT	1140
TGGCTAATGG	AAGAGAAGCT	TGACATGGCC	TTTAGTGAGA	ATAGTCATAA	CATATATAAT	1200
GCTGTGCATG	CCATAGCCCA	TGCCCTCCAT	GAGATGAATC	TGCAACAGGC	TGATAATCAG	1260
GCAATAGATA	ATGGAAAAGG	AGCCAGTTCT	CACTGCTTGA	AGGTAAACTC	CTTTCTAAGA	1320
AGGACCTACT	TCACTAATCC	TCTTGGGGAC	AAAGTGTTTA	TGAAGCAAAG	AGTAATAATG	1380
CAGGATGAAT	ATGACATTGT	TCACTTTGCG	AATCTCTCAC	AACACCTTGG	GATTAAGATG	1440
AAGTTAGGAA	AGTTCAGCCC	ATATTTACCA	CATGGTCGAC	ACTCTCACTT	ATACGTAGAC	1500
ATGATTGAGT	TGGCCACAGG	AAGAAGAAAG	ATGCCATCCT	CTGTGTGCAG	TGCAGATTGT	1560
AGTCCTGGAT	TCAGAAGATT	ATGGAAGGAG	GGAATGGCAG	CCTGCTGTTT	TGTTTGCAGC	1620
CCCTGCCCTG	AAAATGAAAT	TTCTAATGAG	ACAAATATGG	ATCAATGCGT	GAATTGTCCA	1680
GAATACCAAT	ATGCCAACAC	AGAACAGAAC	AAATGTATTC	AGAAAGGTGT	CACCTTCCTA	1740
AGCTATGAAG	ACCCCTTGGG	GATGGCACTT	GCCTTAATGG	CCTTCTGCTT	CTCTGCATTC	1800
ACAGCTGTGG	TACTTTGTGT	CTTTGTGAAG	CACCATGACA	CTCCTATTGT	GAAGGCCAAT	1860
AACAGAAGCC	TCAGCTATCT	ATTACTCATG	TCACTCATGT	TCTGTTTTCT	GTGCTCCTTT	1920
TTCTTCATTG	GCCTTCCAAA	CAAAGTCATC	TGTGTCTTAC	AGCAAATCAC	ATTTGGAATT	1980
GTATTCACTG	TGGCTGTTTC	CACAGTTCTG	GCCAAAACAG	TCACTGTGGT	TCTAGCTTTC	2040
AAAGTCACAG	TCCCAGGAAG	AAGATTGAGA	TACTTCCTTG	TATCAGGGAC	ACTAAACTAC	2100
ATTATTCCTA	TATGTTCCCT	ACTCCAATGT	GTTCTGTGTG	CAATCTGGCT	AGCAGTCTCT	2160
CCTCCCTTTG	TTGATATTGA	TGAACACTCT	CAGCATGGCC	ACATCATCAT	TGTGTGCAAC	2220
AAGGGCTCAG	TTACTGCATT	CTACTGTGTC	CTTGGATACT	TGGCCTGCCT	GGCACTGGGA	2280
AGCTTCACTT	TGGCTTTCTT	GGCCAAGAAT	CTGCCTGATG	CATTCAATGA	AGCCAAGTTC	2340
TTGACCTTCA	GCATGCTAGT	GTTCTGCAGT	GTCTGGGTCA	CCTTCCTCCC	TGTGTACCAT	2400
AGCACAAAGG	GCAAACACAT	GGTTGCTGTG	GAGATCTTCT	CTATCTTGGC	ATCCAGTGCA	2460
GGGATGCTTG	GATGTATTTT	TGTACCCAAG	ATTTATATCA	TTTTAATGAG	ACCAGAGAGA	2520
AATTCTACCC	AAAAGATCAG	AGAAAAATCA	TATTTT			2556

### (2) INFORMATION FOR SEQ ID NO:72:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2169 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

ATCTGTAATG AAGAGAGTAT GTGTTCATTT CTGCTTTCAG GACCCAATTG GGATGAATCT 60 TTAAGTTTCT GGAAGTACCT GGACAGCTTC TTATCTCCAC ATATCCTTCA GCTTTCCTAT 120 GGATCTTTCA GTTCCATCTT CAGTGATGAT GAACAATATC CCTATCTCTA TCAGATGGCC 180 CCAAAGGACA CATCTCTAGC ATTGGCAATG GTCTCCTTCA TACTTTATTT GAAATGGAAT 240 TGGATTGGCC TTGTCATCCC AGATGACGAT CAAGGAAACC AATTTCTTTT AGAGTTGAAG 300 AAACAGAGTG AAAACAAAGA AATTTGCTTT GCCTTTGTGA AAATGATATC TGTTGATGAA 360 GTTTCATTTC CACAAAAAC TGAAATATAC TACAAACAAA TTGTGAAGTC ATTAACAAAT 420 GTTATTATCA TTTATGGAGA AACATATAAT TTCATTGATT TGATCTTCAG AATGTGGGAA 480 CCTCCCATTT TACAGAGAAT ATGGATCACC ACAAAACAAT TGAATTTCCC TACCAGTAAG 540 ACAGACATAA GTCATGACAC ATTCTATGGA TCACTTACTT TTCTACCCCA CCATGGTGAG 600 ATTTCTGGCT TTAAAAATTT TGTACAGACA TGGTTCCATC TCAGAAACAC AGATTTATAT 660 CTAGTAATGC CAGAGTGGAA ATATATTAAC TCTGAAGACT CAGCATCTAA TTGTAAAATA 720 CTGAAGAACA GTTCATCTGA TGCCTCATTT GATTGGCTAA TGGAACAGAA GCTTGACATG 780 GCCTTTAGTG ATAATAGTCA TAACATATAT AATGTTGTGC ATGCCATAGC CCATGCCCTC 840 CATGAGATGA ATCTGCAACA GGCTGATAAT CAGGCAATAG ATAATGGAAA AGGAGCCAGT 900 TCTCACTGCT TGAAGGTAAA CTCCTTTCTA AGAAGGACCT ACTTCACTAA TCCTCTTGGG 960 GACAAAGTGT TTATGAAGCA AAGAGTAATA ATGCAGGATG AATATGACAT TGTTCACTTT 1020 GCGAATCTCT CACAACACCT TGGGATTAAG ATGAAGTTAG GAAAGTTCAG CCCATATTTA 1080 CCACATGGTC GACACTCTCA CTTATACGTA GACATGATTG AGTTGGCCAC AGGAAGAAGA 1140 AAGATGCCAT CCTCTGTGTG CAGTGCAGAT TGTAGTCCTG GATTCAGAAG ATTATGGAAG 1200

	CAGCCTGCTG			CTGAAAATGA		1260
GAGACAAATA AACAAATGTA	TTCAGAAAGG	CGTGAATTGT		AATATGCCAA AAGACCCCTT	CACAGAACAG GGGGATGGCA	1320 1380
CTTGCCTTAA		CTTCTCTGCA		TGGTACTTTG	TGTCTTTGTG	1440
AAGCACCATG ATGTCACTCA	ACACTCCTAT		AATAACAGAA TTTTTCTTCA		TCTATTACTC AAACAAAGTC	1500 1560
ATCTGTGTCT	TACAGCAGAT		ATTGTATTTA	CTGTAGCTGT	TTCCACAGTT	1620
CTGGCCAAAA	CAGTCACTGT		TTCAAAGTCA TACATTATTC	CAGACCCAGG	AAGAAGATTG CCTACTCCAA	1680 1740
TGTGTTCTGT	GTGCAATCTG	GCTAGCAGTC		TTGTTGATAT	TGATGAACAC	1800
	GCCACATCAT	CATTGTGTGC		CAGTTACTGC	ATTCTACTGT	1860
GTCCTTGGAT	ACTTGGCCTG ATGCATTCAA	CCTGGCACTG TGAAGCCAAG	GGAAGCTTCA TTCTTGACCT	CTTTGGCTTT	CTTGGCCAAG AGTGTTCTGC	1920 1980
AGTGTCTGGG	TCACCTTCCT	CCCTGTGTAC		AGGGCAAACA		2040
GTGGAGATCT AAGATTTATA	TCTCCATCTT	GGCATCCAGT GAGACCAGAG	GCAGGGATGC AGAAATTCTA	TTGAATGTAT	TTTTGTACCC CAGGGAAAAA	2100 2160
TCATATTTC						2169

## (2) INFORMATION FOR SEQ ID NO:73:

- (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 1889 base pairs(B) TYPE: nucleic acid

  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GAATTCGGCT	TCTGCACCAA	ATGGCGACGA	AAGACACATC	TCTTTCACTT	GCCATTGTTT	60
CTTTGATGGT	TCATTTTAGG	TGGTCTTGGG	TTGGTCTAAT	TCTCCCAGAT	GACCACAAAG	120
GAAATAAAAT	ACTATCAGAT	TTTAGAAAGG	AGATGGAAAG	AAAAAGAATC	TGTACGGCTT	180
TTGTAAAAAT	GATTCCTGCC	ACATGGACTT	CATCTTTTGT	CAAATTCTGG	GAAAATATGG	240
ATGACACCAA	CATAATAATT	ATTTATGGTG	ACATTGATTC	TCTAGAAGGT	CTAATGCGAA	300
ATATTGGGCA	AAGGTTATTG	ACATGGCATG	TCTGGGTCAT	GAACATTGAA	CCCCATATTA	360
TTGAATATGA	TAATTATTTC	ATGTTAGATT	CATTCCATGG	AAGTTTAATT	TTTAAGCACA	420
ATTATAGAGA	GAATTTTGAG	TTTACCAAAT	TTATTCGAAC	AGTTAATCCT	AAAAAATACC	480
CAGAAGACAT	TTATCTCCCT	AAGATGTGGT	ATTTGTTCTT	CATGTGCTCA	TTTTCTGATA	540
TTAATTGTCA	AGTTTTGGAC	AGCTGTCAAA	CAAATGCTTC	TTTGGATATG	TTACCTAGTC	600
AGATATTTGA	TGTGGTCATG	AGTGAAGAGA	GCACAAGTAT	TTACAATGCT	GTGTACGCTG	660
TGGCTCACAG	CCTCCATGAG	ATGAGACTTC	AGCAACTTCA	AACACAACCG	TGTGAAAATG	720
AAGAAGGGAT	GGAGTTCTTT	CCATGGCAGC	TTAATACTTT	CCTGAAGGAT	ATTGAGGTGA	780
GAGTCAACAG	TTTAGACTGG	AGACAGAGAA	TAGATGCTGA	ATATGACATT	CTTAACCTCT	840
GGAATTTACC	AAAGGGTCTT	GGACTAAAAG	TGAAAATAGG	AAACTTTTAT	GCAAATGCTC	900
CCCAGGGTCA	ACAATTGTCT	TTATCTGAAC	AGATGATTCA	ATGGCCAGAA	ATATTTTCAG	960
AGATCCCTCA	GTCGGTGTGC	AGTGAGAGTT	GTGGGCCTGG	ATTCAGGAAA	GTAACCCTGG	1020
AGAATAAGGC	TATCTGCTGC	TACAATTGTA	CTCCCTGTGC	AGACAATGAG	ATTTCTAATG	1080
AGACAGATGT	AGACCAGTGT	GTGAAGTGTC	CAGAGAGTCA	TTATGCAAAT	ACAGAGAAGA	1140
GCAACTGCTA	TCAAAAGTCT	GTGAGCTTTC	TGGGCTATGA	AGACCCTTTG	GGGATGGCTC	1200
TAGCCAGCAT	AGCTTTGTGC	TTGTCTGCAC	TAACTGCCTT	TGTTATTGGC	ATATTTGTGA	1260
AACACAAAGA	CACTCCTATT	GTTAAGGCCA	ATAATCAAGC	TCTGAGTTAC	ACTTTGCTCA	1320
TCACACTCAA	ATTCTGTTTC	CTATGTTCTT	TGAACTTCAT	TGGTCAGCCC	AACACAGTTG	1380
CCTGCATCCT	TCAGCAGACC	ACCTTTGCAG	TTGCTTTCAC	TATGGCTCTT	GCCACTGTGT	1440
TGGCCAAAGC	TATCACTGTG	GTTCTTGCCT	TTAAGGTCAG	TTTTCCAGGG	AGAATGGTAA	1500
GATGGCTAAT	GATATCAAGG	GGTCCAAACT	ATATCATTCC	TATCTGCACC	CTGATCCAAC	1560
TTCTTCTTTG	TGGAATATGG	ATGGCAATAT	CTCCACCATA	CATTGACCAA	GATGCTCATA	1620
TTGAACATGG	TCACATCATC	ATTTTGTGCA	ACAAGGGCTC	AGCTGTTGCC	TTCCACTCTG	1680
TCCTGGGATA	CCTCTGCTTC	TTGGCCCTTG	GGAGTTATAC	CATGGCCTTC	TTGTCAAGAA	1740
ATTTGCCTGA	TACATTCAAC	GAATCCAAAT	TTATCTCACT	AAGTATGCTG	GTATTCTTCT	1800
GTGTCTGGAT	CACCTTTCTT	CCTGTCTACC	ACAGCACTAA	AGGGAAGGTC	ATGGTCGCCG	1860
TCGAGGTCTT	TTGCATCCAA	GCCGAATTC				1889

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1889 base pairs

  - (B) TYPE: nucleic acid (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GAATTCGGCT	TCTGCATCAA	ATGGCGACGA	AGGACACATC	TCTTTCACTT	GCCATTGTTT	60
CTTTGATGGT	TCATTTTAGG	TGGTCTTGGG	TTGGTCTAAT	TCTCCCAGAT	GACCACAAAG	120
GAAATAAAAT	ACTATCAGAT	TTTAGAAAGG	AGATGGAGAG	AAAAAGAATC	TGTACGGCTT	180
TTGTAAAAAT	GATTCCTGCC	ACATGGACTT	CATCTTTTGT	CAAATTCTGG	GAAAATATGG	240
ATGACACCAA	CATAATAATT	ATTTATGGTG	ACATTGATTC	TCTAGAAGGT	CCAATGCGAA	300
ATATTGGGCA	AAGGTTATTG	ACATGGCATG	TCTGGGTCAT	GAACATTGAA	CCCCATATTA	360
TTGAATATGA	TAATTATTTC	ATGTTAGATT	CATTCCATGG	AAGTTTAATT	TTTAAGCACA	420
ATTATAGAGA	GAATTTTGAG	TTTACCAAAT	TTATTCGAAC	AGTTAATCCT	AAAAAATACC	480
CAGAAGACAT		AAGATGTGGT	ATTTGTTCTT	CATGTGCTCA	TTTTCTGATA	540
TTAATTGTCA	AGTTTTGGAC	AGCTGTCAAA	CAAATGCTTC	TTTGGATATG	TTACCTAGTC	600
AGATATTTGA	TGTGGTCATG	AGTGAAGAGA	GCACAAGTAT	TTACAATGCT	GTGTACGCTG	660
TGGCTCACAG	CCTCCATGAG	ATGAGACTTC	AGCAACTTCA	AACACAACCG	TGTGAAAATG	720
AAGAAGGGAT	GGAGTTCTTT	CCATGGCAGC	TTAATACTTT	CCTGAAGGAT	ATTGAGGTGA	780
GAGTCAACAG	TTTGGACTGG	AGACAGAGAA	TAGATGCTGA	ATATGACATT	CTTAACCTCT	840
GGAATTTACC	AAAGGGTCTT	GGACTAAAAG	TGAAAATAGG	AAACTTTTAT	GCAAATGCTC	900
CCCAGGGTCA	ACAATTGTCT	TTATCTGAAC	AGATGATTCA	<b>ATGGCCAGAA</b>	ATATTTTCAG	960
AAGTCCCTCA	GTCTGTGTGC	AGTGAGAGTT	GTAGGCCTGG	<b>ATTCAGGAAA</b>	GTATCCCTGG	1020
ATGATAAGGC	CATCTGCTGC	TACAAGTGCA	CTCCTTGTGC	CGACAATGAG	ATATCTAATG	1080
AGACAGATGT	AGACCAGTGT	GTGAAGTGTC	CAGAGAGTCA	TTATGCAAAT	ACAGAGAAGA	1140
GCAACTGCTT	CCCAAAATCT	GTGAGCTTTC	TGGCCTATGA	AGACCCCTTG	GGGATGGCTC	1200
TAGCCAGCAT	AGCTTTGTGC	TTATCTGCAC	TCACTGTCTT	TGTTATTGGC	ATCTTTGTGA	1260
AAAACAGAGA	CACTCCTATT	GTCAAGGCCA	ATAATCGGAC	TCTAAGTTAC	ATTTTGCTCA	1320
TCACACTCAC	CTTTTGTTTC	TTATGTTCTT	TGAACTTCAT	TGGTCAGCCC	AACACAGCTG	1380
CCTGCATCCT	TCAGCAGACC	ACCTTTGCAG	TTGCTTTCAC	TATGGCTCTT	GCCACTGTGT	1440
TGGCCAAAGC	TATTACTGTA	GTCCTTGCCT	TTAAGATCAG	TTTTCCAGGG	AGAATGTTAA	1500
GGTGGCTAAT	GATATCAAGG	GGTCCAAGAT	ACATCATTCC	TATCTGCACA	CTGATCCAGC	1560
TTCTTCTTTG	TGGAATATGG	ATGGCAACTT	CTCCACCATT	CATTGACCAA	GATGTTAATA	1620
CTGAAGATGG	ATACATCATC	CTTTTGTGCA	ACAAGGGCTC	AGCTGTTGCC	TTCCATTCAG	1680
TCCTGGGATA	CCTCTGTTTC	TTGGCCCTTG	GGAGTTATAC	CATGGCCTTC	TTGTCTAGAA	1740
ATTTGCCTGA	TACATTCAAT	GAATCCAAAT	TTCTGTCATT	CAGTATGCTG	GTGTTCTTCT	1800
GTGTCTGGGT	CACCTTTCTT	CCTGTCTACC	ACAGCACTAA	AGGGAAAGTT	ATGGTCGTCG	1860
TCGAAGTCTT	CTGCATCCAA	GCCGAATTC				1889

- (2) INFORMATION FOR SEQ ID NO:75:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 270 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

ATGAAGAAGC TCTGTGCTTT	CACGATTTCA	TTGTTGTTTC	TGAAGTTTTC	TCTCATCTTG	60
TGCTGTTGGA GTGAACCAAG	TTGCTTTTGG	AGGATAAAGA	ATAGTGATGA	TAATGACGGA	120
GATTTGCAAA GGGAATGTCA	TTTTTACCTT	GGGGCAGCTG	ATACACCAGT	TGAAGATAAT	180
TTTTATAGTT CACTTTTAAA	ATTTAGGTTT	TCTTTGGACC	ATTTAATCCT	AACCTACGCG	240
ACCATGACCG GCTGCCCCAT	GTCCATCAGG				270

- (2) INFORMATION FOR SEQ ID NO:76:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1308 base pairs

- 183 -

- (B) TYPE: nucleic acid (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

ATGAAGAAGC	TCTGTGCTTT	CACGATTTCA	TTGTTGTTTC	TGAAGTTTTC	TCTCATCTTG	60
TGCTGTTGGA	GTGAACCAAG	TTGCTTTTGG	AGGATAAAGA	ATAGTGATGA	TAATGACGGA	120
GATTTGCAAA	GGGAATGTCA	TTTTTACCTT	GGGGCAGCTG	ATACACCAGT	TGAAGATAAT	180
TTTTATAGTT	CACTTTTAAA	ATTTAGAATT	GCAGCAAGTG	AATATGAGTT	TCTTCTCGTA	240
ATGTTTTTTG	CTATCGATGA	GATCAACAGG	AATCCTTATC	TTTTACCCAA	CATAACTTTG	300
ATGTTCTCCT	TCATTGGTGG	AAACTGTCAG	GATTTATTGA	GAGTTATGGA	CCAAGCATAT	360
ACACAAATAA	ATGGACATAT	GAATTTTGTT	AATTATTTCT	GTTATTTAGA	TGATTCATGT	420
GCCATAGGTC	TTACAGGACC	ATCATGGAAA	ACTTCCTTAA	AACTGGCAAT	GCACTCTTCG	480
ATGCCACTGG	TTTTCTTTGG	ACCATTTAAT	CCTAACCTAC	GCGACCATGA	CCGGCTGCCC	540
CATGTCCATC	AGGTAGCCCC	CAAGGACACA	CATTTGTCCC	ATGGCATGGT	CTCCTTGATG	600
TTTCACTTTA	GATGGACTTG	GATAGGAATG	GTCATCTCAG	ATGATGACCA	GGGTATTCAG	660
TTTCTCTCAG	ATTTAAGAGA	AGAAAGCCAA	AGGCATGGGA	TCTGTTTAGC	TTTTGTTAAT	720
ATGATCCCAG	AAAACATGCA	GATATACATG	ACAAGGGCTA	CAATATATGA	TCAACAAATT	780
ATGACATCTT	CAGCAAAGGT	TGTTATCATT	TATGGTGAAA	TGAACTCTAC	TCTAGAAGTA	840
AGCTTTAGAA	GATGGGAAGA	GTTAGGTGCT	CGGAGAATCT	GGATCACAAC	CTCACAATGG	900
GATGTCATCA	CAAATAAAAA	AGACTTCACC	CTTAATCTCT	TCCATGGGAC	TATCACTTTT	960
GCACACCACA	GAGTTGAGAT	TCCTAAATTA	AATAAATTCA	TGCAAACAAT	GAACACTGCC	1020
AAATACCCAG	TAGATATTTC	TCATACTATA	TTGGAGTGGA	ATTATTTAA	TTGTTCAATA	1080
TCTAAGAACA	GCATTAGAAT	GCATCATATT	ACATTCAACA	ACACCTTGGA	ATGGACATCA	1140
CTGCACAACT	ATGATATGGC	GATGAGTGAT	GAAGGTTACA	GTTTATATAA	TGCTGTTTAT	1200
GCTGTGGCCC	ACACCTACCA	TGAATACATT	TTTCAACAAG	TAGAGTCTCA	GAAAAAGGCA	1260
AAACCCAAAA	GATATTTCAC	TGCTTGTCAG	CAGATATGGA	ACAGTGTG		1308

- (2) INFORMATION FOR SEQ ID NO:77:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1296 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

ATGAAGAAGC	TCTGTGCTTT	CACTATTTCA	TTTTTGTCTC	TGAAGTTTTC	TCTCATCTTG	60
TGCTGTTTGA	CTGAAGCAAG	TTGCTTTTGG	AGGATAAAGA	ATAGTGAAGA	TAGTGATGGA	120
GATTTGCAAA	GAGAATGTCA	TTTTTACCTT	TGGGTAATTG	ATAAACCTAT	TGAAGATAAT	180
TTTTATAATT	CAGTTTTAAA	TTTTAGAATA	TCAGCAAGTG	AATATGAGTT	TCTTCTGGTA	240
ATGTTTTTTG	CTACTGATGA	GATCAACAAG	AATCCTTATC	TTTTACCCAA	CATAACTTTG	300
ATATTCAGCA	TCGTTGGTGG	TCACTGTCAT	GATTTATTGA	GAGGTCTGGA	TCAATCATAT	360
ACACAAATAA	ATGGACGTGT	GAATTTTGTT	AATTATTTCT	GTTATTTAGA	TGATTCATGT	420
AACATAGGCC	TTACAGGACC	<b>ATCATGGAAA</b>	AAATCCTTAA	AACTGGCAAT	GGATTCTTCA	480
ATACCAATGG	TTTTCTTTGG	ACCATTTAAT	CCTAACCTAC	GCGACCATGA	CCGGCTGCCC	540
CATGTCCATC	AGGTAGCCCC	CAAGGACACA	CATTTATCCC	ATGGCATGGT	CTCCTTGATG	600
TTTCATTTTA	GATGGACTTG	GATAGGACTG	GTCATCTCAG	ATGATGACCA	GGGTATTCAG	660
TTTCTCTCAG	ATTTAAGAGA	AGAAAGCCAA	AGGCATGGGA	TCTGTTTAGC	TTTTGTTAAT	720
ATGATCCCAG	AAAACATGCA	GATATACATG	ACAAGGGCTA	CAATATATGA	TAAACAAATT	780
ATGACATCTT	CAGCAAAGGT	TGTTATCATT	TATGGTGAAA	TGAACTCTAC	TCTAGAAGTA	840
AGCTTCAGAA	GATGGGAAGA	TTTAGGTGCT	CGGAGAATCT	GGATCACAAC	CTCACAATGG	900
GATATCATAT	TAAATAAAA	AGAATTCACT	CTTAATCTCT	TCCATGGCCC	TATCACTTT	960
GCACACCACA	AAGTTGAGAT	TCCTAAATTA	AGGAATTTTA	TGCAAACAAT	GAACACTGCC	1020
AAATACCCAG	TAGATATTTC	TCATACTATA		ATTATTTTAA	TTGTTCAATC	1080
TCTAAGAACA		GGATCTTTTT		ACACATTGGA	ATGGACAGCA	1140
CTGCACAACT		CATGAGTGAT		ATTTGTATAA		1200
	ACACCTACCA			TAGAGTCTCA		1260
	GATATTTCAC		CAGATA	INGROTOTOR	GRAAAAGGIA	1296
	CALALITORC	-0-1-191CAG	CUCKIN			1270

## (2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1521 base pairs
- (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: CDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

ATGAAGAAGC	TCTGTGCTTT	CACTATTTCA	المالية	שייייייייייייייייייייייייייייייייייייי	TOTAL TOTAL	
TGCTGTTTGA	CTGAAGCAAG			ATAGTGAAGA		60
GATTTGCAAA				ATAAACCTAT		120
TTTTATAATT			TCAGCAAGTG		TGAAGATAAT	180
ATGTTTTTTG					TCTTCTGGTA	240
ATATTCAGCA				TTTTACCCAA		300
		TCACTGTCAT		GAGGTCTGGA		360
	ATGGACGTGT		AATTATTTCT	GTTATTTAGA	TGATTCATGT	420
AACATAGGCC		ATCATGGAAA			GGATTCTTCA	480
ATACCAATGG	TTTTCTTTGG	ACCATTTAAT	CCTAACCTAC	GCGACCATGA	CCGGCTGCCC	540
CATGTCCATC		CAAGGACACA	CATTTATCCC	ATGGCATGGT	CTCCTTGATG	600
TTTCATTTTA		GATAGGACTG	GTCATCTCAG	ATGATGACCA	GGGTATTCAG	660
TTTCTCTCAG		AGAAAGCCAA	AGGCATGGGA	TCTGTTTAGC	TTTTGTTAAT	720
ATGATCCCAG	AAAACATGCA			CAATATATGA		780
ATGACATCTT	CAGCAAAGGT	TGTTATCATT			TCTAGAAGTA	840
AGCTTCAGAA	GATGGGAAGA	TTTAGGTGCT		GGATCACAAC	CTCACAATGG	900
GATATCATAT	TAAATAAAA	AGAATTCACT		TCCATGGCCC	TATCACTTT	960
GCACACCACA	AAGTTGAGAT		AGGAATTTTA		GAACACTICC	1020
AAATACCCAG	TAGATATTTC	TCATACTATA		ATTATTTTAA		
TCTAAGAACA		GGATCTTTTT		ACACATTGGA-		1080
CTGCACAACT	ATGATATGGC	CATGAGTGAT				1140
GTTGCGGCCC	ACACCTACCA			ATTTGTATAA		1200
GAACACAACA			CTTCAACAAG			1260
TTTACGAACC		TGTTTGTCAG		CCTTGATGAA		1320
	CGGTTGGAGA			GGGAAAATCA	GTGTACAGAG	1380
TATGATATTT	TCATCATTTG	GAATTTTCCA			GAAAATAGGA	1440
AGCTATATAC	CTTGTTTTCC	AAAGAGTCAA	CAACTTCATA	TATCTGATGA	TTTGGAATGG	1500
GCCATGGGAG	GAACATCAAT	A			•	1521
_						

- (2) INFORMATION FOR SEQ ID NO:79:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 933 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single

  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

TCTGCACTTT	CACTATTTCA	TTGTTGTTTC	TGAAGTTTTC	TCTCATCTTG	60
GTGAACCAAG	CTGCTTTTGG	AGGATAAAGA	AGAGTGAAGA	TAATGATGGA	120
GGGAGTGTCA	TTTTTACCTT	TGGAAAACTG	ATGAACCTAT	TCAACATACT	180
ATGATTTAAG	יייי ע עיי עייייייי	GCAGGAAGTG	AATATCACCAC	TGAAGAIAGI	
	11111010111	CAGGAAGIG	MAINIGAGCI	TCTTCTGGTA	240
CTACTGATGA	GATCAACAAG	AATCCTTATC	TTTTACCCAA	CATGAGTTTG	300
TCATTGGTGG	AAACTGTCAT	GATTTATTGA	GAAGTCTGGA	TCAAGAATAT	360
ATGGACATAT	GAATTTTGTT	AATTATTTCT	CHAPALALVCV	ער אייייי ער אייייי ער אייייי	420
mm> a> aa> aa			GILLILIAGA	IGNIICAIGI	420
TTACAGGACC	ATCATGGAAA	ACATCCTTAA	AACTGGCAAT	GCATTCTTCA	480
TTTTCTTTGG	ACCATTTAAT	CCTAACCTAC	GCGACCATGA	CCGGCTGCCC	540
ACCTACCCCC	CAACCACACA	Chmmanaaa	10000100		
MGGIMGCCCC	CHAGGACACA	CATTIGICCC	ATGGCATGGT	CTCCTTGATG	600
GGTGGACTTG	GATAGGACTG	GTCATCTCAG	ATGATGATCA	GGGTATTCAG	660
<b>ልጥጥጥል አር</b> አርል	ACAAACCCAA	ACCOMPCCCA	monommon o o		
AT I I MONON	MONMAGCCAM	MOGCAIGGGA	TCTGTTTGGC	TTTTGTTAAT	720
AAAACATGCA	GATATACATG	ACAAGGGCTA	CAATATATGA	TACACAAATT	780
CAGCAAAGGT	שני א שני א מיצוי א מיצוי	MARCORCA CA	TOTAL COMMON C		
CAGCAMOGI	TGITALCATT	IAIGGIGACA	IGAACTCTAC	TCTAGAAGCA	840
	GTGAACCAAG GGGAGTGTCA ATGATTTAAG CTACTGATGA TCATTGGTGG ATGGACATAT TTACAGGACC TTTTCTTTGG AGGTAGCCCC GGTGGACTTG ATTTAAGAGA AAACATGCA	GTGAACCAAG CTGCTTTTGG GGGAGTGTCA TTTTTACCTT ATGATTTAAG TTTTTAGAATT CTACTGATGA GATCAACAAG TCATTGGTGG AAACTGTCAT ATGGACATAT GAATTTTGTT TTACAGGACC ATCATGGAAA TTTTCTTTGG ACCATTTAAT AGGTAGCCCC CAAGGACACA GGTGGACTTG GATAGGACTG ATTTAAGAGA AGAAAGCCAA AAAACATGCA GATATACATG	GTGAACCAAG CTGCTTTTGG AGGATAAAGA GGGAGTGTCA TTTTTACCTT TGGAAAACTG ATGATTTAAG TTTTTAGAATT GCAGGAAGTG CTACTGATGA GATCAACAAG AATCCTTATC TCATTGGTGG AAACTGTCAT GATTTATTGA ATGGACATAT GAATTTTGTT AATTATTTCT TTACAGGACC ATCATGGAAA ACATCCTTAA TTTTCTTTGG ACCATTTAAT CCTAACCTAC AGGTAGCCCC CAAGGACACA CATTTGTCCC GGTGGACTTG GATAGGACTG GTCATCTCAG ATTTAAGAGA AGAAAGCCAA AGGCATGGGA AAAACATGCA GATATACATG ACAAGGGCTA	GTGAACCAAG CTGCTTTTGG AGGATAAAGA AGAGTGAAGA GGGAGTGTCA TTTTTACCTT TGGAAAACTG ATGAACCTAT ATGATTTAAG TTTTAGAATT GCAGGAAGTG AATATGAGCT CTACTGATGA GATCAACAAG AATCCTTATC TTTTACCCAA TCATTGGTGG AAACTGTCAT GATTTATTGA GAAGTCTGGA ATGACATAT GAATTTTGTT AATTATTCT GTTATTTAGA TTTTCTTTTGG ACCATTTAAT CCTTAACCTAC GCGACCATGA AGGTAGCCCC CAAGGACACA CATTTGTCCC ATGGCATGGT GGTGGACTTG GATAGGACTG GTCATCTCAG ATGATGATCA ATTTAAGAGA AGAAAGCCAA AGGCATGGGA TCTGTTTGGC AAAACATGCA GATATACATG ACAAGGGCTA CAATATATGA	AGGTAGCCCC CAAGGACACA CATTTGTCCC ATGGCATGGT CTCCTTGATG

WO 99/00422 PCT/US98/13680

- 185 -

#### AGCTTTAGAA GATGGGAAGA GTTAGGTGCT CGGAGAATCT GGATCACAAC CACACAATGG 900 GATGTCATCA CAAATAAAAA AAGACTTCAC CCT 933

- (2) INFORMATION FOR SEQ ID NO:80:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1236 base pairs

  - (B) TYPE: nucleic acid (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GCAAGTTGCT	TTTGGCGGAT	AAAGAATAGT	GAAGATAATG	ATGGAGATTT	GCAAAGGGAA	60
TGTCATTTTT	ACCTTGGGGC	AGTTGATAAA	CCAATTGAAG	ATAATTTTTA	TAATTCACTT	120
TTAAAGTTTA	GAATTGCAGC	AAGTGAATAT	GAGTTTCTTC	TGGTAATGTT	TTTTGCTACT	180
GATGAGATCA	ACAAGAATCC	TTATCTTTTA	CCCAACATAA	CTTTGATGTT	CTCCATCATT	240
GGTGGAAACT	GTCATGATTT	ATTGAGAGGT	TTGGATCAAG	CATATACACA	AATAAATGGA	300
CATATGAATT	TTGTTAATTA	TTTCTGTTAT	TTAGATGATT	CATGTGCCAT	AGGTCTTACA	360
GGACCATCAT	GGAAAACATC	CTTAAAACTG	GCAATGCATT	CTTCAATGCC	ACTGGTTTTC	420
TTTGGATCAT	TTAATCCTAA	CCTACATGAC	CATGACCGGC	TGCACCATGT	CCATCAAGTA	480
GCCACCAAGG	ACACACATTT	GTCCCATGGC	ATTGTCTCCT	TGATGTTTCA	TTTTAGATGG	540
ACTTGGATAG	GACTGGTCAT	CTCAGATGAT	GACAAGGGTA	TTCAGTTTCT	CTCAGATTTA	600
AGAGAAGAAA	GCCAAAGGCA	TGGGATCTGT	TTAGCTTTTG	TTAATATGAT	CCCAGAAAAC	660
<b>ATGCAGATAT</b>	ACATGACAAG	GGCTACAATA	TATGATAAAC	AAATTATGAC	GTCTTTAGCA	720
AAAGTTGTTA	TCATTTATGG	TGAAATGAAC	TCTACACTAG	AAGTAAGCTT	TAGAAGATGG	780
GAAAATTTAG	GTGCTCGGAG	AATCTGGATC	ACAACCTCAC	AATGGGATGT	CATCACAAAT	840
TAAAAAAAA	TCACCCTTAA	TCTCTTCCAT	GGGACTATTA	CTTTTGCACA	CCGCAGATTT	900
GAGATTCCTA	AAATTTAAAA	ATTTATGCAA	ACAATGAACA	CTGCCAAATA	CCCAGTAGAT	960
ATTTCTCATA	CTATATTGGA	GTGGAATTAT	TTTAATTGTT	CAATCTCTAA	GAACAGCAGT	1020
AAAATGGATC	ATATTACATT	CAACAACACA	TTGGAATGGA	CAGCACTGCA	CAACTATGAT	1080
<b>ATGGTGATGA</b>	GTGATGAAGG	TTACAATTTG	TATAATGCTG	TTTATGCTGT	GGCCCACACC	1140
TACCATGAAC	ATATTTTTCA	ACAAGTAGAG	TCTCAGAAAA	AGGCAAAACC	CAAAAGATTT	1200
TTCACTGTTT	GTCAGCAGCA	GATATGGAAC	AGTGTG			1236

- (2) INFORMATION FOR SEQ ID NO:81:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2412 base pairs

  - (B) TYPE: nucleic acid (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

ATGTTCATTT	TCATGGAAGT	CTTCTTCCTC	CTTAATATTA	CACTTCTCAT	GGCCAATTTC	60
ATTGATCCCA	GGTGCTTTTG	GAGAATAAAT	TTGGATGAAA	TAATGGATGA	ATATTTGGGA	120
TTATCTTGTG	CTTTCATCCT	GGCAGCAGTT	CAGACACCCA	TTGAAAATGA	TTATTTCAAC	180
AAGACTCTTA	ATGTTCTAAA	AACAACTAAA	AACCACAAAT	ATGCTTTGGC	ATTGGTGTTT	240
GCAATGGATG	AAATCAACAG	AAATCCTGAT	CTTTTACCAA	ATATGTCTTT	GATTATAAGA	300
TACACTTTGG	GCCGTTGTGA	TGGAAAAACT	GTAATACCTA	CACCATATTT	ATTTCGTAAA	360
AAAAAAGAAA	GCCCTATCCC	TAATTATTTC	TGTAATGAAG	AGACTATGTG	TTCCTATCTG	420
CTTACAGGAC	CCCATTGGGA	GGTATCTTTA	GGTTTCTGGA	AGCACATGAA	CAGCTTCTTA	480
TCTCCACGŢA	TCCTTCAGCT	TACCTATGGA	CCTTTCCACT	CCATCTTCAG	TGATGATGAA	540
CAATATCCCT	ATCTCTATCA	GATGGCCCCA	AAGGACACAT	CTCTAGCATT	GGCAATGGTC	600
TCCTTCATAC	TTTACTTTAG	CTGGAACTGG	ATTGGCCTTG	TCATTCCAGA	TGATGACCAA	660
	TTCTTTTAGA					720
	TGATCTCTGT					780
AACCAAATTG	TGATGTCATC	CACAAATGTT	ATTATCATTT	ATGGAGAAAC	ATACAATTTC	840
,	TCTTCAGAAT					900
AAACAATTGA	ATTTCCCTAC	CAGGAAAAA	GACATAAGTC	ATGGCACATT	CTATGGATCA	960

CTTACTTTTC	TACCCCACCA	TGGTGTGATT	TCTGGTTTTA	AAAATTTTGT	ACAGACATGG	1020
TTCCATCTCA	GAAACACAGA	TTTATATCTA	GTAATGCAAG	AGTGGAAATA	CTTTAACTAT	1080
GAAGACTCAG	CATCTACCTG	TAAAATACTG	AAGAACAATT	CATCTAATGC	CTCATTTGAT	1140
TGGCTAATGG	AACAGAAGTT	TGACATGACC	TTTAGTGAGA	ATAGTCATAA	CATATACAAT	1200
GCTGTGCATG	CCATAGCCCA	TGCCCTCCAT	GAGATGAATC	TGCAACAGGC	TGATAATCAG	1260
GCAATAGACA	ATGGGAAAAA	GGAGCCCAGT	TCCTCCCACT	GCTTGAAGGT	AAACTCCTTT	1320
CTAAGAAGGA	TTTACTTCAC	TAATCCTCCT	GGGGACAAAG	TGTTTATGAA	GCAAAGAGTA	1380
ATAATGCACG	ATGAATATGA	CATTGTTCAC	TTTGTGAATC	TCTCACAACA	CCTTGGGATT	1440
AAGATGAAGT	TAGGAAAGTT	CAGCCCATAT	TTACCACATG	GTCGACACTC	TCACTTATAT	1500
GTAGACAGGA	TTGAGTTGGC	CACAGGAAGA	AGAAAGATGC	CATCCTCTGT	GTGCAGTGCT	1560
GATTGTAGTC	CTGGATTCAG	AAGATTATGG	AAGGAGGGAA	TGGCAGCCTG	CTGTTTTGTT	1620
TGCAGCCCCT	GCCCTGAAAA	TGAAATTTCT	AATGAGACAA	CTGTGGTACT	TTGTGTCTTT	1680
GTGAAGCATC	ATGACACTCC	TATTGTGAAG	GCCAATAACA	GAAGCCTCAG	CTACCTATTA	1740
CTCATGTCAC	TCATGTCCTG	TTTTCTGTGC	TCCTTTTTCT	TCATTGGCCT	TCCAAACAGA	1800
GCCATCTGTG	TCTTACAGCA	AATCACATTT	GGAATTGTAT	TCACTATGGC	TGTTTCCACA	1860
GTTCTGGCCA	AAACAGTCAC	TGTGGTTCTG	GCTTTCAAAG	TCACAGACCC	AGGAAGAAGA	1920
TTGAGAAACT	TCCTGGTATC	AGGAACACCC	AACTACATTA	TTCCCATATG	TTCCCTACTC	1980
CAATGTGTTC	TGTGTGCAAT	CTGGCTAGCA	GTTTCTCCTC	CCTTTGTTGA	TATTGATGAA	2040
CACACTCTCC	ATGGCCACAT	CATCATTGTG	TGCAACAAGG	GCTCAGTTAC	TGCATTCTAC	2100
TGTATCCTAG	GATACTTGGC	CTGCCTGGCA	CTTGGAAACT	TCTCTGTGGC	TTTCTTGGCC	2160
AAGAATCTGC	CTGACACATT	CAATGAAGCC	AAGTTCTTGA	CCTTCAGCAT	GCTAGTGTTC	2220
TGTAGTGTCT	GGGTCACCTT	CCTCCCTGTC	TACCATAGCA	CCAAGGGCAA	ACACATGGTT	2280
GCTGTGGAGA	TCTTCTCCAT	CTTGGCATCC	AGTGCTGGGA	TCCTTGGATG	TATATTTGTA	2340
CCCAAGATTT	ATATCATTTT	AATGAGACCA	GAGAGAAATT	CGACCCAAAA	GATCAGGGAA	2400
AAATCATATT	TC					2412

- (2) INFORMATION FOR SEQ ID NO:82:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 381 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single

  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

TGGGAGT CTTCTTCCTC	CTTAATATTA	CACTTCTCAT	GGCCAATTTC	60
				120
				180
TTCTAAA AACAACTAAA	AACCACAAAT	ATGCTTTGGC	ATTGGTGTTT	240
				300
TTTGTGA TGGAAAAACT	GTAACACCTA	CACCATATTT	ATTTCATAAA	360
CCTATCC C				381
	GCTTTTG GAGAATAAAT ICATCCT GGCGGCAGTT ITCTAAA AACAACTAAA ICAACAG AAATCCTGAT ITTGTGA TGGAAAAACT	GCTTTTG GAGAATAAAT TTGGATGAAA TCATCCT GGCGGCAGTT CAGACACCCA TTCTAAA AACAACTAAA AACCACAAAT TCAACAG AAATCCTGAT CTTTTACCAA TTGTGA TGGAAAAACT GTAACACCTA	GCTTTTG GAGAATAAAT TTGGATGAAA TAACGGATGA FCATCCT GGCGGCAGTT CAGACACCCA CTGAAAAAGA FTCTAAA AACAACTAAA AACCACAAAT ATGCTTTGGC FCAACAG AAATCCTGAT CTTTTACCAA ATATGTCTTT FTTGTGA TGGAAAAACT GTAACACCTA CACCATATTT	FGGGAGT CTTCTTCCTC CTTAATATA CACTTCTCAT GGCCAATTTC FCTTTTG GAGAATAAAT TTGGATGAAA TAACGGATGA ATATTTGGGA FCATCCT GGCGGCAGTT CAGACACCCA CTGAAAAAGA TTATTTCAAC FTCTAAA AACAACTAAA AACCACAAAT ATGCTTTGGC ATTGGTGTTT FCAACAG AAATCCTGAT CTTTTACCAA ATATGTCTTT GATTATAAGA FTTGTGA TGGAAAAACT GTAACACCTA CACCATATTT ATTTCATAAA CCTATCC C

- (2) INFORMATION FOR SEQ ID NO:83:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 228 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

ATGAAAAACC TGTGTGTTTT	CACTCTTTCC	TTTTTCCTCC	TGGAGTTTTC	TCTGATCTTG	60
TGCCATTTGA CTGAACCCAT	TTGCTTTTGG	AGGATAAATA	ATAATGAAGA	TAATGATGGA	120
GATTTGAGAA GTGACTGTGG	TTTTTTCCTT	GCAGCAGTTG	AGGGACCTAC	TGACGACTCT	180
TATAATATCT CTGATCTTAG	GTTTTCTTTG	GACCATTTAA	TCCTAAGC		228

(2) INFORMATION FOR SEQ ID NO:84:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1644 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

ATGTTAGAAT	TGGCCCATGG	CACTCTGACT	TTCTCACCCC	<b>ATCATGGGGA</b>	GATTTCTGAT	60
TTCACAAATT	TTATGCAGGA	AGTCACCCCT	ATCAAGTACC	CAGAAGACAT	TTTTCTTCAC	120
ATCTTGTGGA	ACCAGTATTT	CAATTGTCCA	CTTTTGCATT	CTGAGTGTAA	AATCTTTGAA	180
AACTGTATAC	CCAATGCCTC	TTTGGAATTG	TTGCCAGGGG	GTGTTTTTGA	GCTGGTCATG	240
ACTGAAGAGA	GTTACAATGT	GTACAATGCT	GTGTATGCAG	TGGCCCACAG	TCTCCATGAG	300
AAGGCTCTCC	ATCAAGTAGA	AATTCAACCA	CAGGATAATA	AAGATAGGAC	TATATTATTT	360
CCTTGGCAGC	TTCACCCTTT	TCTGAAGAAC	ATTCAGCTGA	TAAATTCTGT	TGGTGATCGT	420
GTGATTCTGG	ACTGGAAAAA	GAAGACGGAT	ACAGAGTATG	ATATTTCCAA	TATTTGGAAT	480
TTCCCAACAG	GTCTTTCCTT	ATTAGTGAAA	GTGGGTACAT	TTGCTCCAAG	TGCTCCCAAG	540
GGGGAACAAC	TTTCGATATC	TGAACACACA	ATTAACTGGC	CCATAGGATT	TACAGAGATT	600
CCAAAGTCTG	TATGCAGTGA	GAGCTGCAGT	CCTGGACACA	GGAAAGTCAT	CCTGGAGAGC	660
AAGCCTGCCT	GTTGCTTTGA	CTGCACTCCT	TGCCCAGATA	AAGAGATTTC	CAACGAGACA	720
GATGTGGGTC	AGTGTGTGAA	GTGTCCTGAA	TCTCATTATG	CAAATACAGA	GAAGAGTCAC	780
TGCCTGAAGA	AGACTATGAC	CTTTCTGGAT	TATAATGATT	CCTTGGGGAC	GGGACTCACA	840
CTCATGTCTC	TGGGATTCTT	TGTTGTCACA	GGTCTTGTTA	TTGGGGTTTT	TATAATCCAC	900
AGAAACACTC	CAATTGTGAA	GGCCAATAAT	AGATCTCTCA	GTTATATCCT	GCTCATCACT	960
CTCACTCTCT	GTTTCCTTTG	TCCCTTGCTC	TTCATTGGGC	TTCCAAACAC	AGCCACATGT	1020
ATCCTACAGC	AGAACTTGTT	TGGACTTCTC	TTCACTGTGG	CTCTATCCAC	AGTGTTGGCC	1080
AAAACTATCA	CTGTAGTTAT	GGCATTCAAG	ATTACTGCTC	CAGGAAGAAA	GACAAGATGG	1140
TTGCTGATAT	TAAGAGCCCC	TCAGTTCATC	ATTCCACTTT	GTGCCCTGAT	GCAAATCCTT	1200
TTCTCTGGGA	TATGGCTGGG	AACATCTCCT	CCATTTGTTG	ACATGGATGC	TCACTCTGAA	1260
CATGGGCACA	TCATCATTCT	ATGCAACAAG	GGCTCAGCTA	TTGGCTTCTA	CTGTACTCTG	1320
GCCTACCTGG	GAGTCATGGC	CTTTGGTAGT	TACCTCTTGG	CTTTCATGTC	CAGGAATCTT	1380
CCTGACACAT	TTAATGAATC	CAAGGCCCTG	GCTTTCAGCA	TGCTGATGTT	CTGCAGTGTC	1440
TGGGTCACAT	TCCTCCCTGT	CTACCACAGC	ACCACTGGGA	AGGTCAGGGT	GGCTATGGAA	1500
ATGTTTTCTA	TCTTGGCTTC	CAGTGCAAGC	ATTCTAACCC	TAATCTTTGT	CCCTAAGTGC	1560
TACATTGTTT	TGTTCAGACC	AGAGAGGAAC	ATACTTCCTC	TAAACAGAGA	AAAAAGACAG	1620
CATAGGAGTA	AAAATTCTGA	AACA				1644

- (2) INFORMATION FOR SEQ ID NO:85:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2304 base pairs

  - (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

ATGGAGGAAA	TCAACAGGAA	CCCTGATCTT	TTACCAAATA	TGTCTTTGGT	TATAAAACAT	60
ACTTTGAGCT	ATTGTGATGG	AAATACTGCA	GACCATATAT	TTAAAGAAAA	ATTTTATAAG	120
CCTTTACCTA	ATTATGTCTG	TAATGAAGAG	ACTATGTGTT	CATTTATGCT	TATAGGGCTG	180
AATTGGGTAT	TGTCTCTAAC	ACTTTTTAAA	GACTTGGACA	TCTTCTCATT	TCCACGTTTC	240
CTTCAAATTT	CCTATGGACC	TTTCCATTCC	ATCTTCAGTG	ATAATGAACA	ATTTCCATAT	300
CTCTATCAGA	TGACCCCAAA	GGACACATCA	CTAGCATTGG	CAATTGTCTC	CTTCTTACTT	360
TACTTCAATT	GGAACTGGGT	TGGGCTTGTC	<b>ATCTCTGATA</b>	ATGATGAAGG	CAATCAATTT	420
CTCTCAGAGT	TGAAAAAAGA	GACCCAAAAC	AAGGAAATTT	GCTTTGCCTT	TGTTAACATG	480
ATGTCAATCC	ATGAGCATTC	ATCTTATCAA	AAAACTGAAA	TGTACTACAA	TCAAATAGTG	540
ATGTCATCAA	CAAATATTAT	TATCATTTAT	GGGAAAACAA	ACAGTATCAT	TGAATTGAGC	600
TTCAGAATGT	GGGTATCTCC	<b>AGTTATACAG</b>	AGGATTTGGG	TCACAAACTC	AGAGTTGGAT	660
TTCCCGACAA	GTATGAGAGA	CTTCACTCAT	GGCACATTCT	ATGGGACTCT	GACATTTCTA	720
CACCACCATG	GTGAGATTTC	TGGATTTACA	AATTTTTTCG	AGACATGGGA	CCATCTCAGA	780
AGCAGAGATT	TAAATCTATT	AATACCAGAG	TGGAAGTACT	TTAGCTATGA	TGCCTCAGGA	840

- 188 -

TCTAACTGTA	AAATATTGAG	GAACTATTCA	TCCAATGCCT	CATTGGAATG	GATAACAGAA	900
CAGAAGTTTC	ACATGGCCTT	TAATGATTAT	AGTCATAGTA	TATATAATGC	TGTGTATGCC	960
ATGGCCCATG	CCCTCCATGA	GACTAATCTG	CAAGAGGTTG	ATAATAAGGA	AATAAGAAAT	1020
GGGAAAGGAG	CAAGTACTCA	CTGCTTGAAG	GTAAACTCAT	TTCTCAGAAA	GACCCACTTT	1080
ACTAATTCTC	ATGGAGAGAG	AGTGATTATG	AAACAGAGAG	TGAGAGTACA	GGAAGACTAT	1140
GACATTGTTC	ACATTCAGAA	TTTCTCACAA	CACCTTCGGA	TTAAGATGAA	GATAGGAAAG	1200
TTCAGCCCAT	ATTTTACACA	TGGTGGACCC	TTTCACTTAT	ATGAAGACAT	GATTCAGTTG	1260
GCCACAGGAA	GTAGAAAGAT	GCCGTCCTCT	GTGTGCAGTG	CAGATTGTAG	TCCTGGATTC	1320
AGAAAATCCT	GGAAGGAGGG	AATGGCCCCC	TGCTGTTTTA	TTTGCAGCCT	GTGCCCTGAA	1380
AATGAAATTT	CTAATGAGAC	AAATATGGAT	CAATGTGTGA	ATTGTCCAGA	ATACCAATAT	1440
GCCAACACAG	AAAAGAACAA	ATGCATTCAG	AAAGACGTGA	TTTTTCTAAG	CTATGAAGAC	1500
CCCTTGGGAA	TGGCTCTTGC	CTTAATTGCC	TTCTGTTTGT	CTGCATTCAC	AGCTGTGGTA	1560
CTTTGGGTCT	TTGTGAAGCA	CCATGACACT	CCTATTGTGA	AGGCCAATAA	CAGAATCCTC	1620
AGCTACATAT	TAATCATGTC	ACTAATGTTC	TGTTTTCTCT	GCTCCTTTTT	CTTCATTGGC	1680
CATCCTAACA	GAGGTACCTG	TATCTTACAG	CAAATCACAT	TTGGCATTGT	ATTCACTGTG	1740
GCTGTTTCCA	CAGTTCTGGC	CAAAACAATC	ACTGTCATTC	TTGCTTTCAA	ACTCAGAGAC	1800
CCAGGGAGAA	GTTTAAGAAA	CTTCCTGGTA	TCTGGTGCAC	CCAACTACAT	TATTCCTATA	1860
TGTTCCTTAT	TGCAATGTAT	TCTGTGTGCA	ATTTGGCTAG	CAGTTTCTCC	TCCTTTTGTT	1920
GATATTGATG	AACATTCTGA	GCATGGCCAC	ATCATGATTG	TGTGCAACAA	GGGCTCCATT	1980
ATGGCATTCT	ACTGTGTCCT	AGGATACTTG	GCCTGCCTGG	CGCTTGGAAG	CTTCACTACA	2040
GCTTTCTTGG	CAAAGAATCT	GCCAGACACA	TTCAACGAAG	CCAAGTTCTT	GACCTTCAGC	2100
ATGCTAGTGT	TCTGCAGTGT	CTGGGTCACC	TTTCTCCCTG	TGTACCATAG	CACAAGGGGC	2160
AGGGTCATGG	TTGCTGTTGA	GATCTTCTCT	ATCTTGGCAT	CCAGTGCAGG	GATGTTTGGA	2220
TGCATCTTTG	CACCCAAAAT	CTACATCATA	TTAATGAAAC	CAGAAAGAAA	TTCTATACAA	2280
AAGTTCAGGG	AGAAATCATA	TTTC				2304

## (2) INFORMATION FOR SEQ ID NO:86:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2001 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

ATGGCTCCTA	AGGACACATC	TCTGGCACTG	GCCATGGTTT	CTTTGTTTGT	CCATTTCAGC	60
TGGAACTGGG	TAGGAGCTGT	TGTTTCAGAT	GATGACCCAG	GTTATGAATT	TATCTTGGAA	120
TTGAGAAGAG	AAATGCAAAG	GAACAATTTT	TGTTTAGCAT	TTGTGAGTAT	CATTGTTAGT	180
GATGACAATT	TATTTCTGAA	AAGGTATAAT	ATCTATTACA	ACCAGATCAA	GATGTCATCA	240
GCAAAAGTTG	TTATCATTTA	TGGAGACAAA	GACTCTCCTC	TACAGGTGAA	CTTTAGACTA	300
TGGAATTTAT	TTGATATCCA	AAGAATCTGG	GTCACTACTT	CACAGTGGGA	TATGATCATA	360
AATAATGGAA	AATTCCTCCT	TAATTCCTTC	TATGGGACTC	TCAGTTTTTC	ACATCACTAT	420
TCTGAATTAT	CTGGTTTTAA	AACATTTATC	CAGACAGCAT	ACCCTTCAAA	CTACAGTGAT	480
GACTTTTCTC	TTGGTATATT	ATGGTGGGTG	TATTTTAATT	GTTCTTTGTC	ATTATCTGAA	540
TGTAAGAATC	TGCAAAATTG	TCCAAAGGAA	AACATATTTA	GATGGTTATA	CAGGCACCAT	600
TTTGAAATGT	CTTTGAGTGA	TACTACTTAT	GACCTATATA	ATTCTATGTA	TGCTGTGGCT	660
TACACACTCC	AACAGATGCT	TCTGAAACAA	GCAGATACAT	GGCAAATAGA	TGATGGAAAA	720
GAACCAGAAT	TTGACTCTTG	GCAGATGCTC	TCTTTCCTGA	GAAATATCCA	ATTTATAAAC	780
CCTGTTGGTG	ACAAAGTGAA	CCTGAATCAT	GAAGAAAAAC	TGGATACAAA	GTATGAGATT	840
CACCAGACTT	TGACTTTTTT	GCCAAATCCT	GTATTTAAGC	TGAAAATAGG	AACATTTTCC	900
CAAAACTTAT	CACATGGTCG	ACAATTATAT	ATGTTGAAAG	AAATGATAGA	GTGGAACACA	960
GGCCACCAAC	AGTCTCCAAC	CTCAGTTTGC	AGTATTCCTT	GTAGTCCAGG	ATTCAGAAAA	1020
TCCCCTCAGC	TGGGAAAGCC	TGTTTGCTGT	TTTGATTGTA	CACCCTGCCC	AGAAAATGAA	1080
ATTTCCAACA	TGACAAACAT	GAATCAATGT	ATCAAGTGTC	TAAATGATCA	GTATGCCAAT	1140
CCTGGAGGAA	CTCGCTGCCT	CAAAAAAGTT	ATTGTATTCC	TGGGTTATGA	AGATCCATTG	1200
GGAATGTCTC	TGGCTATCTT	GGCTCTGTGC	TTCTCTGCTC	TCACAGCTTT	TGTACTTAGT	1260
ATCTTTTTGA	AGCACCAAGA	AACACCCACT	GTCAAGGCCA	ATAATAGAAC	TCTCAGCTAT	1320
GTTCTACTCA	TCTCCCTCAT	CTCTTGTTTT	CTCTGCTCCT	TGCTCTTCAT	TGGTCATCCC	1380
AGCTTTACCA	CATGTATCAT	GCAGCAGACC	ACATTTGCTG	TTGTGTTCAC	TGTAGCTGCA	1440
TCTACTGTCT	TGGCCAAAAC	AATTATTGTA	ATATTGGCCT	TCAAGGTTAC	TAATACAAGT	1500
AGAAAAATGA		GGTATCAGGG	GCACCTAAAT	TCATCATTCC	AATTTGCACA	1560
ATGATTCAAC	TGATTCTCTG	TGGAATTTGG	CTGGGTACTT	CTCCTCCATT	TGTTGATGCT	1620

- 189 -

GATGGACATG TTGAAA	AAGG CCACATTTTG	ATTTTCTGTA	ACAAAGGTTC	AATTCTTGCT	1680
TTCTATTGTG TCCTGG	GATA CTTAGTCTCC	ATTGCCATTG	CAAGTTTCAC	CCTTGCATTC	1740
TTCGCCAGAA ATCTGC	CCGA CACATTCAAT	GAAGCCAAGT	TCCTAACATT	CAGTATGCTA	1800
GTATTTTGCA GTGTCT	GGGT CACCTTTCTT	CCTGTCTATC	ATAGCACCAA	GGGCAAGTCT	1860
ATGGTGGCTG TGGAAG	STTTT CTGTATATTG	GCCTCTAGTG	CAGGGCTGCT	TTTTTGCATC	1920
TTTGCACCAA AGTGCT	TCAT TATTTTGTTA	AGACCTGAGA	AAAAATCTTT	TCAGAAGTTT	1980
CAGAATATAC ATTCTA	T TAAA				2001

## (2) INFORMATION FOR SEQ ID NO:87:

- (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 2598 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single

  - (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

				•		
ATGTCCAGGC	TCAGAGCAGG	AAAAAATATG	CTCACCTTCA	TTTTACTCTT	CTITCTCCTG	60
AACATTCCAC	TTTTTGTGCC	TAGTTTTATT	TATCCCAGGT	GCTTTTGGAG	TATGAAGAAG	120
AATGAATATC	AGGATAGAAA	CCTGGGAACA	GGTTGTATGT	TCTTTATTCT	AGCAGTGCAA	180
CAGCCTATGG	AAAAAGAGTA	TTTCAGTCAT	ATTTCGAATA	TACAAACACC	TACTGAAAAC	240
CAAAAGTATC	CTCTCACCTT	GGCTTTTTCC	ATGAATGAAA	TCAACAACAA	CCCTGATCTT	300
TTGCCAAATA	TGTCTTTAGC					360
CACAAAAGAT	TATTTAATTT	TTCTTTAAAA	AATCATGAAA	TTCTCCCTAA	TTTTATCTGT	420
	TCAAGTGTGG					480
CTTCATATAA	TCCTAAACAA	TTTCATATTT	CAGCAGTTCC	GTCAGCTTAC	TTATGGACAC	540
TTTCATCCTG	CTCTGTGTGA	TCATGAAAAT	TTTCCTCATC	TATATCAGAT	GGCCTCTGAT	600
	TAGCCCTTGC			ATTTCAGTTG		660
GGGTTGGCCA	TCTCAGACAA	TGATCAAGGC	ATACATTTTC	TCTCTTATTT	GAGAAGAGAG	720
ATGGAAAAA	ATACAGTCTG	CTTTGCCTTT	GTCAACATTA	TTCCAGTCAA	TATGAATTTA	780
TACATGTCAA	GAGCTGAAGT	GTATTACAGC	CAAGTTATGA	CATCATCCGC	AAATGTTGTT	840
ATCATTTATG	GTGATACAGG	GAATACGTTA	GCTGTGAGCT	TTAGAATGTG	GGACTCTCTA	900
	GACTATGGGT					960
TTCACATTTG	ATAATGGATA	TGGAACTTTT	GGTTTTGGAC	ACCGCCACAG	TGAGATTTCT	1020
GGTTTTAAAT	ATTTTGTTCA	GACATTGAAC	CCTTTCAAAT	ACTCAGATGA	ATATTTGGTA	1080
AAGCTGGAAT	GGATGTATGT	TAATTGTAAA	ATCTTAGAAT	ATAACTGTAA	GTCACTGAAG	1140
AACTGCTCCT	TTAATCACTC	ATTGGAATGG	CTAATGACAC	ATACTTTTGA	CATGGCCATT	1200
	GTTATGAAAT					1260
ATGACTCTTC	AAAATGTTGA	TAATGTTCTC	CTTCCCAATT	ATGAAGAACA	AAATTATAAT	1320
TGCAAGATGG	TTTATTCCTT	TCTGAGCAAG	ACTCAATTCA	CAAATCCTGT	TGGAGACACT	1380
GTGAATATGA	ATCAAAGAAA	CAAACTGAAG	GAAGAGTACG	ACATTTTCTA	CAATTGGAAT	1440
TTTCCACAGG	GACTTGGATT	TAAAGTGAAA	ATAGGAATAT	TTAGTCCATA	TTTTCCAAAA	1500
GGTCAACAGC	TTCATTTATC	TGAAAATCTG	ATAGAGTGGT	CCACAGGACG	TATACAGATG	1560
CCAACCTCTG	TGTGCAGTGC	CGATTGTGGT	CCTGGATTTA	GGAAAGTCTG	GAAGAATGGA	1620
ATGCCAGCCT	GTTGTTTTGA	CTGCAGTCCC	TGCCCAGAAA	ATGAAATTTC	TAATGAGACA	1680
AATGTGGAAT	TGTGTGTCCA	GTGTCCAGAG	GACCAATATG	CTAACCAAGA	GCAGAATCAC	1740
TGCATTCACA	AAGCTCGTAT	CTTTCTCTCT	TATGATGAAC	CCTTGGGGAT	GGCTCTTTCC	1800
TTAATGGCCT	TATGCCTCGC	TGCACTCACA	GTTGTGGTTC	TTGGAGTCTT	TGTGAAACAT	1860
CACAGAACTC	CCATAGTTAA	GGCCAATAAC	TGCACTCTCA	CCTACATCTT	GCTCATCGCA	1920
CTCATCTTTT	GTTTCCTCTG	CCCCTTGTTC	TTCATTGGCC	ATCCAAACTC	AGCTACCTGC	1980
ATCCTTCAGC	AAATCACATT	TGGAGTTGTG	TTCACTGTGG	CTATTTCCAC	TGTGTTGGCC	2040
AAAACAACCA	CTGTCATTCT	GGCTTTCAGA	GTCACAGCCC	CTCATAGAAT	GATGAAGTAC	2100
TTTCTTGTTT	CAAGGGCATC	TAACTACATC	ATTCCCATTT	GTACTCTCAT	TCAAATTATT	2160
GTATGTGCCA	TCTGGCTAGG	AGCTTCTCCT	CCTTCTGTTG	ATATTGATGC	ACAGTCTGAG	2220
CATGGTCACA	TCATCATTGC	TTGCAACAAG	GGTTCAGTCA	CTGCTTTTTA	CTGTGTCCTG	2280
GGATATCTGG	CCTGCCTGGC	CTTTGTGAGC	TTCACCCTGG	CTTTCCTTTC	CAGAAACCTG	2340
	TCAATGAAGC					2400
	TCCTACCTGT		ACCAAAGGCA	AGGTTATGGT	GGCTGTTGAG	2460
ATCTTTTCCA	CCTTGGCTTC	TAGTGCAGGA	ATGTTGGGAT	GCATTTTTGC	TCCAAAATGC	2520
TACACAATAC	TGTTTAGACC	AGACAGAAAT	TCTCTTCAAA	TGATCAGGGA	GAAGTCATCT	2580
TCTCATACTC	ACATTTTA					2598
					•	

### (2) INFORMATION FOR SEQ ID NO:88:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2337 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: CDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

ATGAGGTTTG	CCATTGAGGA	AATCAACAGC	AATCCCCATC	TTTTACCAAA	CACATCCCTG	60
GGATTTGAGA	TCAATAATGT					120
TCACTTTCAG				GTGCAAGTGA		180
GCTGCTGTAC	TTACAGGACC	ATCGTGGACA	ATATCTGAAT	GCGTAGGGAC	ACTCCTGGAT	240
CTTTACAAAT	TTCCACAGCT	TACTTTTGGG	CCTTTTGATA	GTCTCCTGAG	TGAACAAAGA	300
CGGTTTTCTT	CTCTGTACCA			TTCTGACGCC		360
TCTTTGATGC	TTCATTTCCA	CTGGAACTGG	GTGGGGTTAT	TCATCATAGA	TGATGACAAA	420
	CACTGTCAGA		GAGATGGATA	AAAATGGAGT	CTGCACAGCA	480
TTTGTAGAAA	TGATCCCAGT	CATCAAGGGT	TCATTTTTTA	CCAAATCCTG	GAAAAATCAT	540
GTGCAGATCC	TGGAATCATC	ATCAAATGTG	ATTATTATTT	ATGGGGACTC	TGATTCTCTA	600
TTAAGCTTAA	TAGTAAATAT	TAAGCAGAAG	TTGCTCACAT	GGAAAGTGTG	GGTACTGATC	660
TCACAGTGGG	ATGTTTCTAA	ATTTGATGAT	TATTTCATGG	TAGACTCATT	GCATGGAGCT	720
CTTATTTTTT	CACACCATCG	TGAGGAGATT	CCTAATTTTA	CAGATTTTAT	GCAGAAGTAC	780
AACCCTTCCA	AGTACCCGGA		CTTCATGTAT		GTACTTCAAT	840
TGCTCATTTG	TTAAGAAAGA	TTGTAAAATT	GTGCACAACT	GTTTGCCTAA	TGCCTCCCTG	900
GGGTTCTTGC	CTGGGAACAT	ATTTGACATG	GCCATGAGTG	AAGAGAGTTA	CAATGTATAC	960
	ATGCTGTGGC					1020
CAAACTCATG	AAAAAGGAAA	AAAGATGGTA	TTCTTTCCTT	GGCAGCTTCA	CCCCTTTCTA	1080
AGGGAAAGAC	AACTCATCAA	TCAGAATGGA	GCGAATGAAG	ATCTGGATTG	TACCAGGAAG	1140
TCACATGTAG	AGTATGACAT	TCTCAACTTT	TGGAATTTCC	CAAAAGGTCT	TGGGCTAAAT	1200
GTGAAAGTAG	GAACGTTTTC	TCCAAGTGCT	CCAAAGGAAC	AGAAACTGTC	CATATCTTCT	1260
AACATGATAC	AGTGGGCCAC	AGGGTCGACA	GAGATTCCAC	<b>AGTCTGTATG</b>	CAGTGAGAGC	1320
TGTCATCCTG	GATTCAGGAA	AACCCACCAG	GAAGGCAGGG	TTGCCTGTTG	CTTTGACTGC	1380
ATTCCTTGTC	CAGAAAATGA	GATCTCCAAT	GAGACAGATG	TGGATCAGTG	TGTGAAGTGT	1440
CCAGAAACTC	ACTATGCAAA	CATAGAGAAG	ATCCACTGCC	TACAGAAAAC	TGTGACATTT	1500
CTGTACTATG	ATGACCCATT	GGGGAAGACA	CTTTGCTTCA	TGTCCCTGGG	TTTCTCCTCA	1560
	CTGTTCTTGT				TGTCAAGGCC	1620
AATAACCTGG	CTCTCAGTTA	CACCCTGCTC	ATCACTTTGA	TGCTCTGTTT	TCTCTGTCCC	1680
TTGCTCTTCA	TTGGCCGTCC	CAGCACAGCC	TCCTGTATCC	TGCAGCAAAA	CATTTTTGGG	1740
	CTGTGGCTCT			CTATCACTGT	GGTTATAGCC	1800
	CTTCTCCAGG			TGATATCAAG	GGCCCCTAAT	1860
	CCTTATGCAC			CTGGAATTTG	GCTGACAACC	1920
TCTCCTCCAT	TTATTGATAA	AGATGCTCAC	TCAGAACATG	GACACATCAT	CATCATTTGC	1980
AATAAAGGCT	CAGCTGTTGC	TTTCCATTGC	AACCTTGGAT	ACCTGGGAGC	ACTAGCCCTA	2040
	TTATGGCTTT				TGAAGCCAAG	2100
	TCAGCATGCT			TCACCTTCCT	CCCTGTCTAC	2160
CACAGCACCA	AGGGGAAGAA	CATGGTGGCT	ATGGAAGTCT	TCTCTATCTT	GGCTTCCAGT	2220
	TAGGCATCAT					2280
AGGAATTCAC	TTAGCTATAT	CAGGGACAAA	ACATATGCTA	AAAGCATAAA	ACCTTCT	2337

- (2) INFORMATION FOR SEQ ID NO:89:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1650 base pairs (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

ATGCCTACGG	AAAACGATTA	TTTCAACCAG	ACTCTGAATA	TCCTAAAAAC	AACAAAAAAC	120
CACAAATATG	CTTTGGCATT	GGCCTTTTCA	ATTGATGAAA	TCAACAGGAA	TCCTGATCTT	180
TTACCAAATA	TGTCTTTGAT	CATAAAATAC	CCTTTGGGCC	TTTGCGATGG	ACAAACTACA	240
TTACCTACAC	CCTATTTATT	TAATGAAATA	TATTTTAGGC	CTATCCCTAA	TTATTTCTGT	300
AATGAAGAGA	CTATGTGTAC	ATTTCTACTT	ACAGGACCGC	ATTGGATAAC	ATCTTATAGT	360
TTCTGGATAC	ACTTGAACAT	CTTCTTATCT	CCTAGTATGA	ACCCAAAGGA	CACATCCCTA	420
GCTTTGGCAA	TGGTCTCCTT	CTTACTTTAT	TTCAAGTGGA	ACTGGGTCGG	CCTTGTCATC	480
TCAGATGATG	ATCAAGGCAA	TCAATTTCTC	TCTGAGTTGA	AAAAAGAGAG	CAAAATCAAG	540
GAAATTTGCT	TTGCATTTGT	GAGCATGCTG	GCAATCGATG	AGATTTCATT	TTATCATAAA	600
ACTGAAATGT	ACTACAACCA	AATTGTGATG	TCATCCACAA	ACGTTATTAT	CATTTATGGG	660
AAAACAGAGA	GTATTATTGA	GTTGAGCTTC	AGAATGTGGG	AATCTCCAGT	TATCCAGAGA	720
<del>-</del>	CCACAAAAGA	AATGAATTTC	CCTACCAGTA	AGAGAGATTT	AACTCATGAC	780
ACATTCTATG	GGACTCTTAC		AGCCATGGGG	AGATTTCAGG	CTTTAAAAAT	840
TTTGTACAGA	CATGGTACCA	TCTTAGAATC	ACTGATTTGC	ATCTAGTAAT	GCCAGAGTGG	900
AAATATTTTA	ACTATGAAGC	CTCAGCATCT	AACTGTAAAA	TATTGAAGAA	CTATTCATCC	960
AGTGCCTCAT	TGGAATGGTT	AATGGAGCAG	ACATTTGACA	TGGTCTTTAG	TGATGGAAGT	1020
CGGGATATAT	ATAATGCTGT	AAATGCCATG	GCCCATGCAC	TCCATGAGAT	GAATCTGCAC	1080
CTGGTTGATA		AGACAATGGG	AAAGGAGCCA	GTTCTCACTG	CTTTAAGATA	1140
AACTCCTTTC	TCAGAAAGAC	CCACTTCACT	AATCCTCTTG	GGGACAGAGT	GATTATGAAA	1200
GAGAGAGAAA		AGACTATAAC	ATTTTTCACA	CTTGGAATTT	TTCTCAGCAC	1260
ATTGGTTTTA	AGGTGAAGAT	AGGAAAGTTC	AGCCCATATT	TTCCACATGG	CAGGCACTTT	1320
CACCTATATG	TAGACATGAT	TGAGTTGGCT	ACAGGAAGTA	GAAAGATGCC	ATCCTCTGTG	1380
TGCACTGAAG	ATTGTAGTCC	TGGATACAGA	AGATTCTGGA	AGGAGGGAAT	GGCAGCCTGC	1440
TGTTTTGTTT	GCAGTCCCTG	CCCTGAAAAT	GCAATTTCTA	ATGAGACAAA	TATGGATCAG	1500
TGTGTGAATT	GTCCAGAATA			GGGACAAATG	CATTCAGAAA	1560
AATGTGATGT	TTCTAAGCTA	CAAAGACCCC	CTTGGGGATG	ACTCTTGCCT	TCATAGCCTT	1620
CTTTTTCTCT	GCATTAACAG	CTGTTGTACT				1650

## (2) INFORMATION FOR SEQ ID NO:90:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2379 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

ATGATAGTAT	TCTTTCTCCT	CAACATTCCA	CTTCTCATGG	CAAATTCCGT	TGATCCCAGG	['] 60
TGCTTTTGGA	AAATAAATTT	GAATGAAGTC	AAGGATATAG	ATTTAGATAC	AAGTTGTTAC	120
TTCATCCTTG	AGGCAGTTCA			ATTTCAACCA		180
	CAACCAAATA			TAGCCTTTAC		240
ATAAACAGGA	ATCCTCATAT	TTTACCAAAC		TTATAAAACA		300
CACTGTGATG	GAAATATCCC	ACTCCGCTTA			GCCTTTTCCT	360
AATTATGGCT				TTATGGGACC	GAATTTGTGG	420
CCATCTGTAG	ATTTTTTCAT		ATCTTATTTC		TCAGATTTCC	480
TTCGGACCTT	TCCATTCCAT		AATGAACAAT		CTATCAGATG	540
				TCATACTTTA		
AACTGGGTTG	GTCTTGTCCT				CTTCAACTGG	600
				ATCAATTTCT	CACAGAGTTG	660
	CCCACAACAC			TGAACATGAT	GGCAATCAAT	720
GAGAATTCAT		AACTGACATG			GTCAACCGCA	780
AATGTTATTA	TCATTTATGG	GGAACGACCC	AGTATTATTG	AACTGTGTTT	CAGAACATGG	840
ACATCTCCAG	TCATACAGAG	GATATGGGTT	ACCAAATCAG	AGTTGTATTT	CCCAACAAGT	900
AAGAGAGACT	TAAGTCATGG	AACATTCTAT	GGAACTCTAG	CATTTCAACA	ACACCATGAT	960
GTGATTTCTG	GATTTAAAAA	TTTTGTACAG	ACATGGTACC	ATCTCAAAAG	CATGGATTTA	1020
TATTTATTAA	AGCCAGAGTG	GGGTTTCTTT	GAATATGAAA	CCTCAGCATC	TTACTGTAAA	1080
ATACTGATGA	GTAATTCATC	GAATGTCTCA	TTGGAATGGC	TAATGGAACA	GAAGTTTGAC	1140
ATAGCCTTTA	ATGACAATAG	TCATAGTATA	•	TGTACGCCAT		1200
CTCCATGAAA	AGAATCTGAA	ACAAATTGAT	AATCAGGAAA	TCAGCTATGG		1260
AGTACTCACT	GCTTGAAGTT			TCCACTTCAC		1320
GGGGAGAGAG				AAGACTATGA		1380
CTGCAGAACT				TAGGGCAGTT		
- <del>,</del>	GTGGACAATT					1440
TITCHCHIG	GIGGWCWWII	TCACTTATAT	GAAGACATGA	TTGATTTGGC	CACAGGAAGT	1500

		GTGTAGTGCA	GATTGTCGTC	CTGGATACAG	AAAATTCTGG	1560
	TGGCAGCCTG		TGCAGTCCCT	GTCCAGACAA	TGAAATTTCT	1620
AATGAAACAA	CTGTGGTACT	TTGGGTCTTT	GTGAAGCACC	ATGACACTCC	TATTGTGAAG	1680
GCCAATAACA	GAATCCTCAG	CTACATATTA	ATCATGTCAC	TCATGTTCTG	CTTTCTGTGC	1740
TCCTTTTTCT	TCATTGGCCA	TCCTAACAGA	GGTACCTGTA	TCTTACAGCA	AATCACATTT	1800
GGAATTGTAT	TCACTGTGGC	TGTTTCCACA	GTTCTGGCCA	AAACAATCAC	TGTGCTTCTG	1860
		AGGAAGAAAG				1920
AACTACATTA	TTCCCATATG	TTCCCTGTTG	CAATGCACTC	TGTGTGCAAT	TTGGCTAGCA	1980
GTTTCTCCAC	CATTTGTTGA	TATCGATGAA	CATTCTGAGC	ATGGTCACAT	CATAATTGTG	2040
TGCAACAAGG	GATCTGTTAT	GGCATTCTAC		GATATTTGGC		2100
CTTGGAAGTT	TCACGATGGC	TTTCTTGGCA	AAGAATCTGC	CTGACACATT	CAATGAAGCC	2160
AAGTTCTTGA	CCTTCAGCAT	GCTAGTGTTC	TGCAGTGTCT	GGATCACGTT	CCTTCCTGTC	2220
TACCATAGCA	CCAAGGGCAG	AGTCATGGTT	GCTGTTGAAA	TTTTCTCCAT		2280
AGTGCAGGGA	TGCTTGGATG	CGTCTTTGCA	CCCAAAATTT			2340
GAGAGAATTC		ACAGGAGAAA				2379

## (2) INFORMATION FOR SEQ ID NO:91:

#### (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2394 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

#### (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

ATGGTAATAT TCTTCCTTCT CAACATTCCA TTTCTCCTGG CAAATTTCAT GGATCCCAGA TGCTTTTGGA AAATAAATTT GAATGAAATC AAGGATGAAG TCCTTGGGAT GACTTGTTCC 120 TTCATCCTTG AAACAGTTCA GAAGACTATG GACAAAGATT ATTTCAACCA GACTCTGAAT 180 GTCCTAAATA CAACTACAAA CCACAAATAT GCCTTGGCAT TGGCCTTTAC AGTGGATGAA ATCAACAGGA ATCCTGATCT TTTACCAAAT ATGTCTCTGA TTATAAAATA CAATTTGGGT 300 CATTGTGATG GAAAAACTGT AACAACTCTA TCCGATTTAT TTAATCCAAA TAATCATCTC CATTTCCCCA ATTATTTATG TAATGAAGGG ATTATGTGTT TGGTTCTGCT TACAGGACCA 420 CATTGGAGAG CATCTTTATA TCTCTGGATA TCCGTGTATG TCTACCTGTC TCCACATTTC CTTCAGCTTT CCTATGGACC TTTCTACTCC ATCTTCAGTG ATAATGAACA ATATCCTTAT 540 CTCTATCAGA TGGGCCCAAA GGACTCATCA CTAGCATTGG CAATGGTCTC CTTCATAATT 600 TACTTCAAGT GGAACTGGGT TGGGCTATTT ATCTCAGATG ATGATCAAGG CAATCAATTT 660 CTCTCAGAGT TGAAAAAAGA GAGCCAAACC AAGGATATTT GCTTTGCCTT TGTGAACATG ATATCAGTCA GTGATGTTTC ATACTATCAT AAAACTGAAA TGTACTACAA CCAAATTGTG 780 ATGTCATCCA CAAAGGTTAT TATCATTTAT GGGGAAACAA ACAGTATTAT TGAATTGAGC 840 TTCAGAATGT GGTCATCTCC AGTTAAACAG AGAATATGGG TCACCACAAA ACAATTTGAT 900 TGCCCTACCA GTAAGAGAGA CTTAACTCAT GGCACATTCT ATGGGACCCT TACATTTCTA 960 CACCACTATG GTGAGATTTC TGGCTTTAAA AATTTTGTAC AGACACGGTA CAATCTCAGA AGCACAGATT TATATCTAGT AATGCCAGAG TGGAAATATT TTAACTATGA AGCCTCAGCA 1020 1080 TCTAACTGTA AAATACTGAG AAACTATTTA TCCAATATCT CACTGGAATG GCTAATGGAA 1140 CAGAAATTTG ACATGTCATT TAGTGATTAT AGTCACAACA TATACAATGC TGTATATGCC 1200 ATTGCTCATG CACTCCATGA GAAGAATCTG CAAGAAGTTG AAAATCAGGC AATAAACAAT GCGAAAGGAG AAAATACTCA CTGCTTGAAG CTAAACTCAT TTCTGAGAAA GACCCACTTC 1320 ACTAATTCTC TTGGGAACAG AGTAATTATG AAACAGAGAG AAGTAGTGCA TGGAGACTAT AATATTGTTC ACATGTGGAA TTTCTCACAA CGCCTTGGGA TTAAGGTGAA GATAGGACAA TTCAGCCCAC ATTTTCCACA GGGTCAACAG TTACACTTAT ATGTAGACAT GACTGAGTTG GCTACAGGAA GTAGAAAGAT GCCATCCTCA GTGTGCAGTG CAGATTGCCA TCCTGGATTC AGAAGAATCT GGAAGGAGGA AATGGCAGCC TGCTGTTTTG TTTGCAACCC CTGCCCTGAA 1560 1620 AATGAAATTT CTAATGAGAC GATGGTGGTA TTTTGGGTCT TCGTGAAGCA CCATGACACT 1680 CCTATTGTGA AGGCCAATAA CAGAATCCTC AGCTACCTAT TAATCGTGTC ACTCATGTTC 1740 TGTTTTCTGT GCTCCTTTTT CTTCATTGGC TATCCTAACA GAGCAACCTG TATCTTACAG 1800 CAAATCACAT TTGGAATCTT CTTTACTGTG GCTATTTCCA CAGTTCTGGC CAAAACAATC 1860 ACTGTGGTTC TGGCTTTCAA AGTCACAGAC CCAGGAAGAC AATTAAGAAT CTTTTTGGTA 1920 TCGGGGACAC CCAACTACAT TATTCCCATA TGTTCCCTAT TGCAATGTAT TCTGTGTGCA 1980 ATCTGGCTAG CAGTTTCTCC TCCCTTTGTT GATATTGATG AACACTCTGA GCATGGCCAC 2040 ATCATCATTG TGTGCAACAA GGGCTCCATT ACTGCATTCT ACTGTGTCCT GGGATACTTG 2100 GCCTGCCTGG CCTTTGGAAG CTTCACTATA GCTTTCTTGG CAAAGAACCT GCCTGACACA 2160 TTCAACGAAG CCAAGTTCTT GACCTTCAGC ATGCTAGTGT TCTGCGCTGT CTGGGTCACC 2220

- 193 -

TTCCTCCCTG TCTACCATAG CACCAAGGGC AAGGTCATGG TTGCTGTGGA GATCTTCTCC 2280 ATCTTGGCAT CTAGTGCAGG GATGCTGGGA TGCATCTTTG CACCCAAAGT TTACATCATT
TTAATGAGAC CAGACAGAAA TTCGATCCAC AAAATCAGGG AGAAATCATA TTTC 2340 2394

- (2) INFORMATION FOR SEQ ID NO:92:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2085 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

GTCTACCTGT	CTCCACATTT	CCTTCAGCTT	TCCTATGGAC	CTTTCTACTC	CATCTTCAGT	60
GATAATGAAC	AATATCCTTA	TCTCTATCAG	ATGGGCCCAA	AGGACTCATC	ACTAGCATTG	120
GCAATGGTCT	CCTTCATAAT	TTACTTCAAG	TGGAACTGGG	TTGGGCTATT	TATCTCAGAT	180
GATGATCAAG	GCAATCAATT	TCTCTCAGAG	TTGAAAAAAG	AGAGCCAAAC	CAAGGATATT	240
TGCTTTGCCT	TTGTGAACAT	GATATCAGTC	AGTGATGTTT	CATACTATCA	TAAAACTGAA	300
ATGTACTACA	ACCAAATTGT	GATGTCATCC	ACAAAGGTTA	TTATCATTTA	TGGGGAAACA	360
AACAGTATTA	TTGAATTGAG	CTTCAGAATG	TGGTCATCTC	CAGTTAAACA	GAGAATATGG	420
GTCACCACAA	AACAATTTGA	TTGCCCTACC	AGTAAGAGAG	ACTTAACTCA	TGGCACATTC	480
TATGGGACCC	TTACATTTCT	ACACCACTAT	GGTGAGATTT	CTGGCTTTAA	AAATTTTGTA	540
CAGACACGGT	ACAATCTCAG	AAGCACAGAT	TTATATCTAG	TAATGCCAGA	GTGGAAATAT	600
TTTAACTATG	AAGCCTCAGC	ATCTAACTGT	AAAATACTGA	GAAACTATTT	ATCCAATATC	660
TCACTGGAAT	GGCTAATGGA	ACAGAAATTT	GACATGTCAT	TTAGTGATTA	TAGTCACAAC	720
ATATACAATG	CTGTATATGC	CATTGCTCAT	GCACTCCATG	AGAAAGATCT	GCAAGAATTT	780
GAAAATCAGG	CAATAAACAA	TGCGAAAGGA	GAAAATACTC	ACTGCTTGAA	GCTAAACTCA	840
TTTCTGAGAA	AGACCCACTT	CACTAATTCT	CTTGGGAACA	GAGTAATTAT	GAAACAGAGA	900
GAAGTAGTGC	ATGGAGACTA	TAATATTGTT	CACATGTGGA	ATTTCTCACA	ACGCCTTGGG	960
ATTAAGGTGA	AGATAGGACA	ATTCAGCCCA	CATTTTCCAC	AGGGTCAACA	GTTACACTTA	1020
TATGTAGACA	TGACTGAGTT	GGCTACAGGA	AGTAGAAAGA	TGCCATCCTC	AGTGTGCAGT	1080
GCAGATTGCC	ATCCTGGATT	CAGAAGAATC	TGGAAGGAGG	AAATGGCAGC	CTGCTGTTTT	1140
GTTTGCAACC	CCTGCCCTGA	AAATGAAATT	TCTAATGAGA	CGAATATGGA	TCAGTGTGCG	1200
AATTGTCCAG	AATACCAGTA	TGCCAACACA	GAAAAGAACA	AATGCATCCA	GAAAGGTGTG	1260
ATTGTTCTAA	GCTATGAAGA	CCCCTTGGGG	ATGGCTCTTG	CCTTAATAGC	ATTCTGTTTC	1320
TCTGCATTCA	CAGTGGTGGT	ATTTTGGGTC	TTCGTGAAGC	ACCATGACAC	TCCTATTGTG	1380
AAGGCCAATA	ACAGAATCCT	CAGCTACCTA	TTAATCGTGT	CACTCATGTT	CTGTTTTCTG	1440
TGCTCCTTTT	TCTTCATTGG	CTATCCTAAC	AGAGCAACCT	GTATCTTACA	GCAAATCACA	1500
TTTGGAATCT	TCTTTACTGT	GGCTATTTCC	ACAGTTCTGG	CCAAAACAAT	CACTGTGGTT	1560
CTGGCTTTCA	<b>AAGTCACAGA</b>	CCCAGGAAGA	CAATTAAGAA	TCTTTTTGGT	ATCGGGGACA	1620
CCCAACTACA	TTATTCCCAT	ATGTTCCCTA	TTGCAATGTA	TTCTGTGTGC	AATCTGGCTA	1680
GCAGTTTCTC	CTCCCTTTGT	TGATATTGAT	GAACACTCTG	AGCATGGCCA	CATCATCATT	1740
GTGTGCAACA	AGGGCTCCAT	TACTGCATTC	TACTGTGTCC	TGGGATACTT	GGCCTGCCTG	1800
GCCTTTGGAA	GCTTCACTAT	AGCTTTCTTG	GCAAAGAACC	TGCCTGACAC	ATTCAACGAA	1860
GCCAAGTTCT	TGACCTTCAG	CATGCTAGTG	TTCTGCGCTG	TCTGGGTCAC	CTTCCTCCCT	1920
GTCTACCATA	GCACCAAGGG	CAAGGTCATG	GTTGCTGTGG	AGATCTTCTC	CATCTTGGCA	1980
TCTAGTGCAG	GGATGCTGGG	ATGCATCTTT	GCACCCAAAG	TTTACATCAT	TTTAATGAGA	2040
CCAGACAGAA	ATTCGATCCA	CAAAATCAGG	GAGAAATCAT	ATTTC		2085

We claim:

10

20

30

## **Claims**

- 1. A family of pheromone receptor polypeptides, each of said polypeptides comprising from amino terminus to carboxyl terminus:
- 5 (a) an amino-terminal extracellular domain containing from 30 to 600 amino acids;
  - (b) a transmembrane region comprising:
    - (i) seven non-contiguous transmembrane domains designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7
    - (ii) three non-contiguous extracellular domains designated EC2, EC3 and EC4, and
    - (iii) three non-contiguous intracellular domains designated IC1, IC2, and IC3,

wherein the transmembrane domains, the extracellular domains and the intracellular domains are attached to one another from amino terminus to carboxyl terminus in the order TM1-IC1-TM2-EC2-TM3-IC2-TM4-EC3-TM5-IC3-TM6-EC4-TM7, and

wherein the transmembrane region has at least about 35% homology and a length approximately equal to a transmembrane region of a polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50; and

- (c) a carboxyl-terminal intracellular domain containing from 5 to 200 amino acids; wherein the pheromone receptor polypeptides are expressed in a Gα_o protein-expressing vomeronasal organ neuron or are expressed in another olfactory organ neuron in an animal which does not possess a vomeronasal organ.
- 2. The polypeptides of claim 1, wherein the transmembrane region of each of said polypeptides has at least between about 60% and about 90% homology to the transdomain region of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50.
- 3. The polypeptides of claims 1 or 2, wherein the non-contiguous intracellular domains of each of said polypeptides has at least between about 60% and about 90% homology to the non-contiguous intracellular domains of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 34, 36, 38, 40, 42, 44, 46, 48, and 50.

5

10

15

WO 99/00422 PCT/US98/13680

4. The polypeptides of claim 1, wherein the extracellular domain of each of said polypeptides has at least between about 50% and about 90% homology to the extracellular domain of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50.

5. The polypeptides of claim 2, wherein the extracellular domain of each of said polypeptides has at least between about 50% and about 90% homology to the extracellular domain of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50.

6. The polypeptides of claim 3, wherein the extracellular domain of each of said polypeptides has at least between about 50% and about 90% homology to the extracellular domain of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50.

- 7. The polypeptides of claims 1 or 2, wherein the extracellular domain contains at least between about 50 and about 500 amino acids.
- 8. The polypeptides of claim 3, wherein the extracellular domain contains at least between about 50 and about 500 amino acids.
  - 9. The polypeptides of claims 4, 5 or 6, further comprising a signal sequence attached to the amino terminus of the extracellular domain.
- 10. The polypeptides of claim 9, wherein the signal sequence is selected from the group of signal sequences of a pheromone receptor polypeptide of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
- 11. A method for identifying a nucleic acid encoding a pheromone receptor polypeptide, comprising:
  - (1) contacting a mixture of nucleic acid molecules with at least one nucleic acid probe of a nucleic acid selected from the group consisting of: (a) a nucleic acid molecule selected from

WO 99/00422 PCT/US98/13680

the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55 that encodes a pheromone receptor polypeptide; (b) a unique fragment of (a); (c) a human homolog of (a) or (b); and (d) a set of degenerate primers of any of (a), (b) or (c); and

- (2) identifying the sequences within the mixture that hybridize to the probe.
- 12. The method of claim 11, wherein the mixture is a genomic library.
- 13. The method of claim 11, wherein the mixture is a cDNA library.

10

5

- 14. The method of claim 11, wherein the nucleic acid probe contains a detectable label.
- 15. The method of claim 11, wherein the at least one nucleic acid probe is a pair of degenerate polymerase chain reaction primers that amplify a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55, the method further comprising the step of subjecting the mixture to a polymerase chain reaction amplification reaction prior to selecting a member of the mixture which hybridizes to the nucleic acid probe.
- 16. The method of claim 15, wherein the pair of degenerate polymerase chain reaction primers is selected from the group consisting of SEQ ID NOs. 60 and 61, SEQ ID NOs. 62 and 63, SEQ ID NOs. 64 and 63, SEQ ID NOs. 64 and 65, and SEQ ID NOs. 66 and 67.
- 17. The method of claim 16, wherein the pair of polymerase chain reaction primers is selected from the group consisting of SEQ ID NOs. 60 and 61, SEQ ID NOs. 62 and 63, SEQ ID and NOs. 64 and 63.

## 18. An isolated nucleic acid molecule

(a) which hybridizes under high or low stringency conditions to a molecule consisting of a nucleic acid sequence selected from the group consisting of SEQ ID NO. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 54, and 55, and which codes for a pheromone receptor,

WO 99/00422 PCT/US98/13680

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

- 197 -

- (c) complements of (a) and (b).
- 5 19. The nucleic acid molecule of claim 18, wherein the pheromone receptor is expressed in the vomeronasal organ or is expressed in another olfactory organ in an animal which does not possess a vomeronasal organ.
- 20. The nucleic acid molecule of claim 18, wherein the pheromone receptor is expressed in a  $G\alpha_0$  protein-expressing vomeronasal organ neuron.
  - 21. The nucleic acid molecule of claim 18, wherein the pheromone receptor is a G-protein coupled receptor.
- 15 22. The isolated nucleic acid molecule of claim 18, wherein the pheromone receptor has an amino acid sequence selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
- 23. The isolated nucleic acid molecule of claim 18, wherein the isolated nucleic acid molecule is selected from the group consisting of SEQ ID NO. 51, 53, 54, 55, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, and 92, that encodes a pheromone receptor polypeptide.
- 24. The isolated nucleic acid molecule of claim 18, wherein the isolated molecule comprises a molecule having a sequence which encodes a pheromone receptor unique fragment, wherein said unique fragment is selected from the group consisting of a pheromone receptor extracellular domain, a pheromone receptor transmembrane domain, a pheromone receptor extracellular domain, a pheromone receptor extracellular domain coupled to at least one transmembrane domain, and at least one pheromone receptor transmembrane domain coupled to a pheromone receptor intracellular domain.

15

25

- 25. The isolated nucleic acid molecule of claim 18, wherein the pheromone receptor extracellular domain, the pheromone receptor transmembrane domain and the pheromone receptor intracellular domain have amino acid sequences selected from the group of sequences identified as these domains in SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
- 26. The isolated nucleic acid molecule of claim 18, wherein the unique fragment is selected from the group consisting of between 12 and 4000, between 12 and 2000, between 12 and 1000, between 12 and 500, between 12 and 250, between 12 and 100, between 12 and 50, and between 12 and 25, nucleotides in length.
- 27. An isolated nucleic acid molecule, comprising
- (a) a molecule having a sequence selected from the group consisting of SEQ ID NO. 51, 53, 54, 55, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, and 92, and which codes for a pheromone receptor;
- (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and
  - (c) complements of (a) and (b).
- 28. An expression vector comprising the isolated nucleic acid molecule of claims 18-27 operably linked to a promoter.
  - 29. A host cell transformed or transfected with the isolated nucleic acid molecule of claims 18-27.
  - 30. A host cell transformed or transfected with the isolated nucleic acid molecule of the expression vector of claim 28.
- An isolated polypeptide encoded by the isolated nucleic acid molecule of claims 18-27.
  - 32. The isolated polypeptide of claim 31, wherein the isolated polypeptide has a pheromone receptor activity.

- 33. The isolated polypeptide of claim 31, wherein the isolated polypeptide comprises a polypeptide selected from group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
- The isolated polypeptide of claim 33, wherein the isolated polypeptide is a fragment of a peptide selected from the group consisting of an extracellular domain, a transmembrane domain and an intracellular domain, wherein the foregoing domains have amino acid sequences selected from the group of sequences identified as these domains of a pheromone receptor polypeptide selected from group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
  - 35. A vaccine containing an isolated polypeptide selected from the group consisting of the isolated polypeptides of claim 31, 32, 33, and 34.
- 15 36. A method for controlling fertility in an animal, comprising:

  administering to an animal in need of such treatment, an effective amount of the vaccine of claim 35 to elicit an immune response to the isolated polypeptide.
- An isolated binding polypeptide which binds selectively to a polypeptide of claim 1, 2,
   4, 5, 6, 8, 10, 31, 32, 33, and 34, provided that the isolated binding polypeptide does not bind to a G-protein coupled receptor other than a Gα₀⁺-coupled pheromone receptor.
- 38. The isolated binding polypeptide of claim 37, wherein the binding polypeptide binds to a polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.
- 39. The isolated binding polypeptide of claim 37, wherein the binding polypeptide is an antibody fragment selected from the group consisting of a Fab fragment, a F(ab)₂ fragment or a fragment including a CDR3 region selective for a pheromone receptor polypeptide.

40. The isolated binding polypeptide of claim 38, wherein the binding polypeptide is an antibody fragment selected from the group consisting of a Fab fragment, a F(ab)₂ fragment or a fragment including a CDR3 region selective for a pheromone receptor polypeptide.

5

## 41. An affinity matrix comprising:

a solid support to which is coupled an isolated binding polypeptide selected from the group consisting of the binding polypeptides of any of claims 37740.

10 42. A method for isolating a pheromone receptor, comprising:

contacting a composition containing a putative pheromone receptor with the affinity matrix of claim 41 under conditions to permit the pheromone receptor to selectively bind to the binding polypeptides coupled to the solid support; and

isolating the polypeptides that bind to the affinity matrix.

15

## 43. A composition comprising:

the polypeptide of claim 1, 2, 4, 5, 6, 8, 10, 31, 32, 33, or 34; and a pharmaceutically acceptable carrier.

20 44. A composition comprising:

the nucleic acid molecule of any of claims 18-28; and a pharmaceutically acceptable carrier.

- 45. A composition comprising:
- 25 the binding polypeptide of claim 37; and a pharmaceutically acceptable carrier.
  - 46. A composition comprising:

the binding polypeptide of claims 38, 39 or 40; and

- a pharmaceutically acceptable carrier.
  - 47. A method for modulating a pheromone receptor activity in a cell, comprising;

10

25

administering to the cell an amount of the isolated binding polypeptide of claim 37 effective to modulate pheromone receptor activity in the cell.

- 48. A method for modulating a pheromone receptor activity in a cell, comprising:

  administering to the cell an amount of the isolated binding polypeptide of claim

  38, 39, or 40 effective to modulate pheromone receptor activity in the cell.
  - 49. The method of claim 47, wherein modulating a pheromone receptor activity comprises reducing the pheromone receptor activity.
  - 50. The method of claim 48, wherein modulating a pheromone receptor activity comprises reducing the pheromone receptor activity.
- 51. The method of claim 47, wherein the pheromone receptor activity is selected from the group consisting of a signal transduction activity and a ligand binding activity.
  - 52. The method of claim 48, wherein the pheromone receptor activity is selected from the group consisting of a signal transduction activity and a ligand binding activity.
- The method of claim 47, wherein the cell is a vertebrate cell, preferably a mammalian cell.
  - 54. The method of claim 48, wherein the cell is a vertebrate cell, preferably a mammalian cell.
  - 55. The method of claim 47, wherein the cell is an invertebrate cell, preferably an insect cell.
  - 56. The method of claim 48, wherein the cell is an invertebrate cell, preferably an insect cell.
- 30 57. A method for reducing the binding of a pheromone having a binding domain to a pheromone receptor having a ligand binding site that selectively binds to the binding domain of the pheromone, comprising:

25

contacting the pheromone receptor with an agent which binds to the binding domain for a time effective to reduce binding of the pheromone to the ligand binding site of the pheromone receptor.

- 5 58. The method of claim 57, wherein the agent is an antibody which binds to the binding domain.
  - 59. A method for decreasing pheromone receptor mediated signal transduction activity in a subject comprising:
- administering to a subject in need of such treatment an agent that selectively binds to an isolated nucleic acid molecule of claim 1 or an expression product thereof, in an amount effective to decrease pheromone receptor mediated signal transduction activity in the subject.
- 15 60. The method of claim 59, wherein the agent is selected from the group consisting of an antisense nucleic acid and a binding polypeptide.
  - 61. A method for identifying lead compounds for a pharmacological agent useful in the diagnosis or treatment of disease associated with pheromone binding to a pheromone receptor polypeptide containing a ligand binding site that selectively binds to a binding domain of the pheromone, comprising

forming a mixture comprising a pheromone receptor polypeptide or unique fragment thereof containing a ligand binding site, a molecule protein containing a binding domain which selectively binds the pheromone receptor ligand binding site, and a candidate pharmacological agent,

incubating the mixture under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of selective binding of the molecule containing a ligand binding domain by the pheromone receptor ligand binding site, and

detecting a test amount of selective binding of the molecule containing the binding domain by the pheromone receptor ligand binding site, wherein reduction of the test amount of selective binding relative to the first amount of selective binding indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which disrupts selective

binding of a molecule containing a binding domain by a pheromone receptor containing a ligand binding site and wherein increase of the test amount of selective binding relative to the first amount of selective binding indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which enhances selective binding of a molecule containing a binding domain by a pheromone receptor polypeptide containing a ligand binding site.

10

20

## **AMENDED CLAIMS**

[received by the International Bureau on 11 December 1998 (11.12.98); original claim 1 amended; remaining claims unchanged (1 page)]

- 1. A family of isolated pheromone receptor polypeptides, each of said isolated polypeptides comprising from amino terminus to carboxyl terminus:
- 5 (a) an amino-terminal extracellular domain containing from 30 to 600 amino acids;
  - (b) a transmembrane region comprising:
    - (i) seven non-contiguous transmembrane domains designated TM1, TM2, TM3, TM4, TM5, TM6 and TM7
    - (ii) three non-contiguous extracellular domains designated EC2, EC3 and EC4, and
  - (iii) three non-contiguous intracellular domains designated IC1, IC2, and IC3, wherein the transmembrane domains, the extracellular domains and the intracellular domains are attached to one another from amino terminus to carboxyl terminus in the order TM1-IC1-TM2-EC2-TM3- IC2-TM4-EC3-TM5-IC3-TM6-EC4-TM7, and

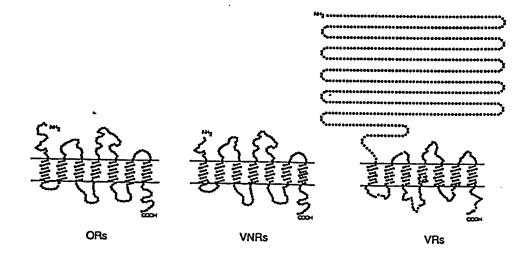
wherein the transmembrane region has at least about 35% homology and a length approximately equal to a transmembrane region of a polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50; and

- (c) a carboxyl-terminal intracellular domain containing from 5 to 200 amino acids; wherein the pheromone receptor polypeptides are expressed in a Gα, protein-expressing vomeronasal organ neuron or are expressed in another olfactory organ neuron in an animal which does not possess a vomeronasal organ.
- 2. The polypeptides of claim 1, wherein the transmembrane region of each of said polypeptides has at least between about 60% and about 90% homology to the transdomain region of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 12, 14, 34, 36, 38, 40, 42, 44, 46, 48, and 50.
- 3. The polypeptides of claims 1 or 2, wherein the non-contiguous intracellular domains of each of said polypeptides has at least between about 60% and about 90% homology to the non-contiguous intracellular domains of a pheromone receptor polypeptide selected from the group consisting of SEQ ID NO. 2, 4, 6, 8, 10, 34, 36, 38, 40, 42, 44, 46, 48, and 50.

# FIBURE 1.

KA KA KA	PROTECTILISTICAN SPIROCAN SELECTION CONTROL SANCTON SELECTION SELE	AX 38
٧x	# MePINGVPPI-VITLINA PIDPACHGRUNDEITDEYLGLICAVITLINA PIDDYFRITINA FITTINA FI	HT HT HT
VX VX: VX: VX:	SENTERINGENCEDLEKSLOGETAGIOGENGTVITTCTLOSCALIGHTGENTALLAN-ESSNEVFF	
VR1 VR2 VR3 VR4 VR5 VR7	elsegnyslnyeraktaguvisdooggyfisleeggregiclapynnyerong tymtratyydrintseakvvityginnitleaspravi Elsegnyslnyeraktaguvisdooggyfisdleesgregiclapynnyerong tymtratyydgithisakvvityginnitleaspravi Elsegnyslnyeraktaguvisdooggyfisdleesgregiclapynnyerong tymtratyydgithisakvvityginnitleaspravi Ellanyspilyloontiguvipodoggyfislingsinnitchavktaguvipyppotytyviytiintiintolykaspravi Ellanyspilyloontiguvipodoggyfislingsinnitchavktaguvipyppotytyviittiintiintiintiintiintiintiintiintiis	ī. P
VRI VR3 VR4 VR5 VR6 VR7	Carinitional incorting gitterentethen colonativatietilentics-ische incolonativatien carinitionalien scholbergien ein er	
VRI VR3 VR4 VR5 VR6 VR7	Vansdegynlynavyavastyheyifoqvesqkulppryftacqqvsslikitavttnpvcelvnourenqcteydifiinnffociglkvkigsyl halsdegynlynavyavastyheyifoqvesqruappryftacqqvsslikitavtnpvgelvnourenqcteydifiinnffociglkvkigsyl halsdeshkithavyavastyhenifoquapaidhkappryffvcqqvsslikitavtnipvcelvnourenqcteydifiinnffociglkvkigsyl kalsdhsenithavyavasliklapproloqadqaidhkcapskaffurthfuldtyppcolvnourenthcoevdyprinnfordelglkvkigstl kalsdhsenithavyavaslikgoloqlotopchiplekkysplhatyttipvcekynkolvnodevdyprinleggleidhkologisy vanseestsithavyavaslikgoloqlotopchiplektprypholifyrdifyrisidmrqridaetdilninnfyrglalkvkighty vanseestsithavyavaslikgoloqlotopchiplektprypholifyrdifyrnisldm	483
VR1 VR2 VR3 VR4 VR5 VR6 VR7	PCFPGRGKLEISDDLEMAKGGTSPOVYSSVCSVACTAGFRKIYGKETADCCFDCVOCPEHEISHETDHEGCVRCPDDKYMIZGTECLSRAVSFLAYE PCFPKSOOLHIADDLEMAMGGTSV-VPSSVCSVACTAGFRKIYGKETADCCFDCVOCPEHEISHETDHEGCVRCPDDKYMIZGTECLSRAVSFLAYE PCFPGRGELEISDLEMAMGGTSV-VPSSVCSADCSPGFRKIYGKETADCCFDCVPGFEHEISHETHEGOCNIGCFPGFWAMHERGUSRAVFFLAYE PYLPHGGHSELYYDMIZELATGRAK-HPSSVCSADCSPGFRKIYGGHACCFVCSPFFREISHETHEGOCNIGCFYTYMTEGHRCIGRGVTFLSYE PYLPHGGHSELYYDMIZELATGRAK-HPSSVCSADCSPGFRKIYGHAMGGHACCFVCSPGFREISHETHEGOCNIGCFYGYTYMTEGHRCIGRGVTFLSYE AMAPGGGGLSLEGMIGMPEIFSE-IPOSVCSESGRPGFRAVILEHRALGCYNGTPCADHEISHETHDOCVRCPESHTAHTERSHCFPKSVSFLAYE AMAPGGGGLSLEGMIGMPEIFSE-VPGSVCSESGRPGFRAVILEHRALGCYNGTPCADHEISHUTDVDGCVRCPESHTAHTERSHCFPKSVSFLAYE	561
VRI VRZ VR3 VR6 VR5 VR6 VR7	DELGNALGCHALSFEATTILILVTPVKYKDTPTVALGRILSYTLLISLVTCFLCSLLFIGPPDQVTCTPQQTTFGVLFTVSVSTVLAKTITVVNAFK DPLGNALGCHALSFEATTILVLVTPVKYKDTPTVALGRILSYTLLISLVTCFLCSLLFIGPPDQVTCTPQQTTFGVLFTVSVSTVLAKTITVVNAFK DPLGNALGCHALSFEATTILVLTFFKKYDDFPTVALGRILSYTLLISLVTCFLCSLLFIGRPDQVTCTLQQTTFGVLFTVSVSTVLAKTITVVNAFK DPLGNALALHAFCFSAFTAVVLCVFVRHBOTPTVALGRSLSYTLLISLUTGFLGSFFFTGGTPRAVICVLQQTTFGVFFVAVSTVLAKTITVVNAFK DPLGNALALHAFCFSAFTAVVLCVFVRHBOTPTVALGRSLSYTLLHSLUTGFLGSFFTTGGTPRAVICVLQQTTFGVFTVAVSTVLAKTVTAVLAFK DPLGNALASIALCLSALTAFVIGTFVRHROTPTVALGRALSTLLSTLLITTFGFLGSHRIGGTPRAVACTLQQTTFAVAFTRALATVLAKTITVVLAFK DPLGNALASIALCLSALTAFVIGTFVRHROTPTVALGRALSTLLSTLLITTFGFLGSHRIGGTPRAVACTLQQTTFAVAFTRALATVLAKTITVVLAFK DPLGNALASIALCLSALTAFVIGTFVRHROTPTVALGRALTVLAKTITVVLAFK	679
VR1 VR2 VR3 VR4 VR5 VR6 VR7	LTPPGENDERLYTGAREVEPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGILALGSTTAPTAREPDTFHEAK VTVPGRELRYFLYSGTLHTISPICTLEGILLGGIRGATSPPFVDIDERSGREHIVGHEGSAVARHVIGTGSLALGSTTAPTAREFDTFHEAK VTVPGRELRYFLYSGTLHTISPICTLEGILLGGIRGATSPPFVDIDERSGREHIVGHEGSAVARHVIGTGSLALGSTTAPTAREFDAFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTAPTAREFDAFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGSTTALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYTISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGGSTALGSTTAPTAREFDTFHEAK VSFPGRURRHRISRGPRYTISPICTLEGILLGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGGSTALGSTTAPTAREFDTFHEAK VSFPGRURRHRITGGIRGATSPPFIDDDVHTEDGTILLGHEGSAVARHVIGTGSLALGGSTALGSTTAPTAREFDTFHEAK VSFPGRURRHRITGGIRGATSPPTAPTAREFDTFHEAK VSFPGRURRHRITGGIRGATSPPTAPTAREFTHEAK VSFPGRURRHRITGGIRGATSPPTAPTAREFTHEAK VSFPGRURRHRITGGIRGATSPPTAREFTHEAK VSFPGRURRHRITGGIRGATSPPTARE	777
VR4 VR5 VR6	PLTF3HLVPCSVMITPLPVTHSTRGKVKVVVEVF3ILASSAGLINGIVVRKCTVILIRPDSHPIKKHKGKLLY- PLTF3HLVPCSVMITPLPVTHSTRGKVKVVVEVF3ILASSAGLINGIVVRKCTVILIRPDSHPIKKHKGKLLY- PLTF3HLVPCSVMITPLPVTHSTRGKVKVVVEVF3ILASSAGLINGIVVRKTVILINFDSHPIRKHKGKLY- PLTF3HLVPCSVMVTPLPVTHSTRGKHKVAVEIF3ILASSAGRIGGEVFRITTILIGPFRHSTQKIRKSTT- PLTF3HLVPCSVMVTPLPVTHSTRGKKKVAVEIF3ILASSAGRIGGEVFRITTILIGPFRHSTQKIRKSTT- PLTF3HLVPCSVMVTPLPVTHSTRGKV PLSSSKLVPPCVMVTPLPVTHSTRGKV PLSSSKLVPPCVMVTPLPVTHSTRGKV	BSO

FIBURE 2.



•								
				11111111	11111111			
. 2442444	1111111	*******	14525141	*******	*****		aasalas.	
-व्यवस्थान स्थान	-=======	: 1535552	*******	*******	444784			
	cectees.	·						
. 134	444-444-	*:  ::::::	*******			****		
leecceeeg	444222			*******	*******			
4444444	******	: ::::::	4440000		444444	· E E E - P E -	22222	
94444444	*******		******		******		124-0-2	EE EE
		*:	EREE-EK-		*****		FFFERRF	
*****	1		********	. 44844444	******		2274.4	
	beesed		*****	- # # # # # # # # # # # # # # # # # # #	******	*******		<- F
ERRERE						.444444		:: ::
****			2224-024		******		4 . 4 4 8 5 .	FF F4
	Dest-re-	- * * * * * * * * * * * * * * * * * * *	244-60F-		******	*4444-44	4.44E8.	
		*********		*******	404647-6			
		• 4444444			******		******	
- Cereera	: cazeaaa		**************************************				FFF#10-	re «r
	Transfer of	*********			2		******	
	4444444	*******		222-2-2-		******	70-4	** **
			17016000	>======		******	1 1	** **
decerri	*******			2		******		** **
	444-4444				21-2722			
			********	2245544 2001	12208422			28 28.
	222222	······	*******				444444	8-
		<=						47
	*******			******		*******	454	*** **
	*******	EECEE-	********	1=1-1 050+0	22204-22			
dercered	,		********	*******	44464-46		******	4
-2333 AAMARKAR				*******			~ = = = = = =	400 80
	444-544				74444447 74847684	444444	<pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre>	
******	*******		********		4442444		454444	
			********	*******	2424422			*** **
			*******	* *******	******		*******	
78845787	-2-4-76-	*******				4448-	6r66r66 364r6	
	4445444	222-2-22			*******	***-**		
****		4004444		********		41-411		444 43
48444	4444444		******	******				176 00
7720477					*******	1644674		
-1- 1				2247274	44444444	*****	*******	
A- E		4		0			44 3 0 2 0 0	444 49
; :					•••••	444444		
772777	1::::::::					224444 244444		
1111111				1001.000	*******			
	444444			*******	*****	RECEBAC	4464474	*** **
	- 242-	*******			*****	*******	,,,,,,,,	
			*******	4477840	*******		E	244 4F
	*********	44-4444		28224022	*****	.444444	*******	
	******				********		*****	E - E E -
	.,,,,,,,,,,	4444444				:	48.0222	222 0-
	*******	1			4548848	444444		444 45
		4444444	*******	********	*******		*******	
		4-444			-4>>=4>>			recer
	********							>4544 PPPPPP
				4444684			44.444	45
	4	444-447-					44.0844	*******
	4444				~~== - = ~	******		
	dere e e e e e				***- ** * *		44.4444	******
	14444444	000-60-6	2.222	******			****	******
				*******		******	*******	******
	1	1111111	BEEREERA	115:115				
	********							-

FIGURE 3.

International application No. PCT/US98/13680

A. CLASSIFICATION OF SUBJECT MATTER  IPC(6) :C07K 14/705; C12N 15/12; A61K 38/17; C12Q 1/68  US CL :536/23.5, 24.31; 530/350; 514/2; 435/6  According to International Patent Classification (IPC) or to both national classification and IPC							
	wed by classification symbols)						
Documentation searched other than minimum documentation to	the extent that such documents are include	ed in the fields searched					
Electronic data base consulted during the international search	(name of data base and miles and t						
APS, Biosis, Medline, WPI		ie, search terms used)					
C. DOCUMENTS CONSIDERED TO BE RELEVANT							
Category* Citation of document, with indication, where	appropriate, of the relevant passages	Relevant to claim No.					
X BROWN et al. Cloning and Chara Ca ²⁺ -Sensing Receptor from Boying	ecterization of an Extracellular	18-21, 24, 26					
Y December 1993, Vol. 366, pages 57.	5-580, pages 577 and 578.	1-17, 22, 23, 25, 27, 43					
Biochemistry. 1996, Vol. 35, No. 5	tion, and Ligand Binding. 0, pages 16077-16084.	1-27, 43					
	C. See patent family annex.						
SCL 356/33, 2431; 530/35, 5142; 435/6  commontation searched (classification system followed by classification symbols)  1.8. 536/33, 2431; 530/350, 514/2; 435/6  commentation searched other than minimum documentation to the extent that such documents are included in the fields searched common taken and the search of the state and the search of the search terms used)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  commentation searched other than minimum documentation to the extent that such documents are included in the fields searched continued the search of the search terms used)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  commentation searched other than minimum documentation to the extent that such documents are included in the fields searched continued the search of the search of the search terms used)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  commentation searched (classification symbols)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  commentation searched (classification symbols)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  commentation searched (classification symbols)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  Commentation searched (classification symbols)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  Commentation searched (classification symbols)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  Commentation searched other than minimum documentation of the search search terms used)  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  1.8. 1536/33, 2431; 530/350, 514/2; 435/6  1.8. 21, 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 24, 26  1.9. 2							
		i					
L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of excellent citetion or other	when the document is taken alone	red to involve an inventive step					
Os document referring to an oral disclosure, use, exhibition or other	combined with one or more other such	step when the document is					
P document published prior to the international filing date but later than the priority date claimed		i					
Date of the actual completion of the international search	Date of mailing of the international sea	rch report					
18 SEPTEMBER 1998		·					
ame and mailing address of the ISA/US	Authorized officer						
BOX PC1	W. Jamence	4					
• 11 • •	i —						

Form PCT/ISA/210 (second sheet)(July 1992)*

International application No. PCT/US98/13680

C (Continua	tion). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant	Relevant to claim No	
Х, Р	HERRADA et al. A Novel Family of Putative Pherom Receptors in Mammals with a Topographically Organiz Sexually Dimorphic Distribution. Cell. 22 August 199 pages 763-773, see pages 765-767.	1-27, 43 (Specie	
Х, Р	MATSUNAMI et al. A Multigene Family Encoding a Array of Putative Pheromone Receptors in Mammals. August 1997, Vol. 90, pages 775-784, pages 776-778.	Diverse Cell. 22	1-27, 43 (species 1 and 4)

International application No. PCT/US98/13680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)							
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:							
1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:							
2. Claims Nos.:  because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:							
3. X Claims Nos.: 28-42, 44-56 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).							
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)							
This International Searching Authority found multiple inventions in this international application, as follows:							
Please See Extra Sheet.							
I. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.							
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.							
As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-27 and 43, species 1, 4, 17, 26-29							
No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:							
Remark on Protest The additional search fees were accompanied by the applicant's protest.							
No protest accompanied the payment of additional search fees.							

International application No. PCT/US98/13680

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-27, 43, drawn to pherome receptor polypeptides and their encoding nucleic acids.

Group II, claims 57 and 58, drawn to a method of reducing the binding of a pheromone to a pherome receptor.

Group III, claims 59 and 60, drawn to a method of decreasing pherome receptor mediated signal transduction.

Group IV, claim 61, drawn to a method of identifying lead compounds.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

```
1) SEQ ID NO: 1 and 2;
 2) SEQ ID NO: 3 and 4;
 3) SEQ ID NO: 5 and 6;
 4) SEQ ID NO: 7 and 8;
 5) SEQ ID NO: 9 and 10;
 6) SEQ ID NO: 11 and 12;
 7) SEQ ID NO: 13 and 14:
 8) SEQ ID NO: 15 and 16;
 9) SEQ ID NO: 17 and 18;
 10) SEQ ID NO: 19 and 20;
 11) SEQ ID NO: 21 and 22;
 12) SEQ ID NO: 23 and 24;
 13) SEQ ID NO: 25 and 26;
 14) SEQ ID NO: 27 and 28;
 15) SEQ ID NO: 29 and 30;
 16) SEQ ID NO: 31 and 32;
17 SEQ ID NO: 33 and 34;
 18 SEQ ID NO: 35 and 36;
19) SEQ ID NO: 37 and 38;
20) SEQ ID NO: 39 and 40;
21) SEQ ID NO: 41 and 42;
22) SEQ ID NO: 43 and 44;
23) SEQ ID NO: 45 and 46;
24) SEQ ID NO: 47 and 48:
25) SEQ ID NO: 49 and 50;
26) SEQ ID NO: 51 and 52;
27) SEQ ID NO: 53;
28) SEQ ID NO: 54;
29) SEQ ID NO: 55;
30) SEQ ID NO: 68:
31) SEQ ID NO: 69;
32) SEQ ID NO: 70:
33) SEQ ID NO: 71;
34) SEQ ID NO: 72;
35) SEQ ID NO: 73;
36) SEQ ID NO: 74;
37) SEQ ID NO: 75;
38) SEQ ID NO: 76;
39) SEQ ID NO: 77;
40) SEQ ID NO: 78;
41) SEQ ID NO: 79;
42) SEQ ID NO: 80;
43) SEQ ID NO: 81;
44) SEQ ID NO: 82;
45) SEQ ID NO: 83;
```

International application No. PCT/US98/13680

```
46) SEQ ID NO: 84;

47) SEQ ID NO: 85;

48) SEQ ID NO: 86;

49) SEQ ID NO: 87;

50) SEQ ID NO: 88;

51) SEQ ID NO: 89;

52) SEQ ID NO: 90;

53) SEQ ID NO: 91;

54) SEQ ID NO: 92.
```

The claims are deemed to correspond to the species listed above in the following manner:

The claims are directed to pheromone receptor polypeptides and their encoding nucleic acids having the recited sequences.

The following claims are generic: 1-27, 43, and 57-61.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: It is noted that the expression "special technical features" is defined in Rule 13.2 as meaning "those technical features that define a contribution which each of the inventions, considered as a whole makes over the prior art". The claimed invention of Group I, directed to a family of pheromone receptor polypeptide, encompasses naturally occurring non-isolated products present in the vomeronasal organ and is anticipated by the prior art (see Dulac and Axel). Therefore, the polypeptide of Group I lacks a special technical feature. The special technical feature of Group II is a method of using a binding protein to reduce the binding of the pheromone receptor to its ligand. The special technical feature of Group III is a method of using a compound that binds to the nucleic acid encoding a pheromone receptor to decrease pheromone receptor mediated signal transduction. The special technical feature of Group IV is a method of identifying lead compounds for a pharmacological agent useful in the diagnosis or treatment of disease associated with pheromone binding to a pheromone receptor. The special technical feature of each group is not the same or does not correspond to the special technical feature of any other group because the methods of Groups II, III, and IV require different starting reagents and method steps to accomplish different goals. The Groups are not linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each of the species has a distinct amino acid sequence and is encoded by a distinct nucleic acid sequence.



International application No.
PCT/US98/13680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)				
This international report has not been established in respect of certain claims under Article 17(2Xa) for the following reasons:				
1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:				
2. Claims Nos.:				
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:				
3. X Claims Nos.: 28-42, 44-56 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).				
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)				
This International Searching Authority found multiple inventions in this international application, as follows:				
Please See Extra Sheet				
· · · · · · · · · · · · · · · · · · ·				
	ĺ			
As all required additional search fees were timely paid by the applicant, this international search report covers all searchal claims.	ble			
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payme of any additional fee.	nt			
3. X As only some of the required additional search fees were timely paid by the applicant, this international search report cover only those claims for which fees were paid, specifically claims Nos.:  1-27 and 43, species 1, 4, 17, 26-29	:13			
-				
4. No required additional search fees were timely said by the				
No required additional search fees were timely paid by the applicant. Consequently, this international search report restricted to the invention first mentioned in the claims; it is covered by claims Nos.:	is			
Remark on Protest The additional search feet were				
The section season sees were accompanied by the applicant's protest.				
No protest accompanied the payment of additional search fees.				